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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

ALEXANDER G. BEARN

CECILIE LEUCHTENBERGER

FRANZ ALTMANN AND JULES G. WALTNER

USE OF STEROIDS IN RHEUMATIC DISEASES

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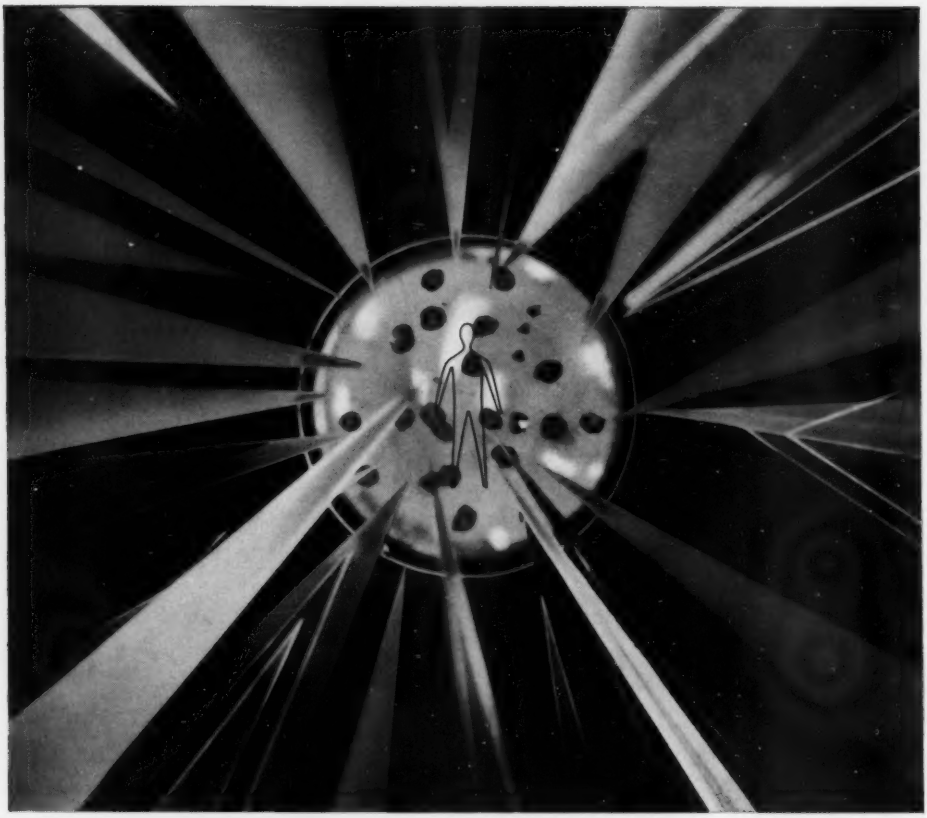

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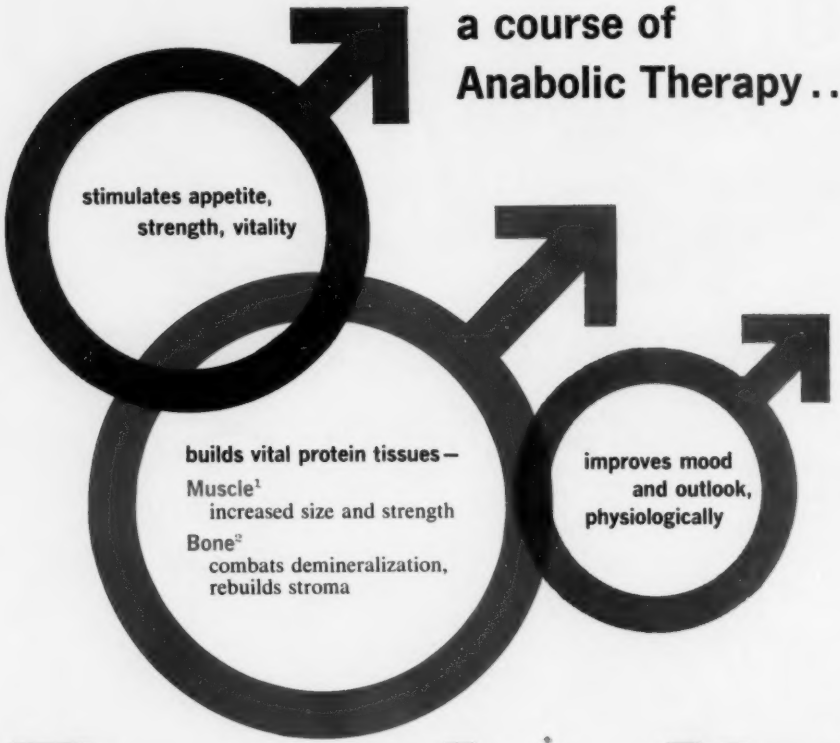

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1. Osol, A. and Farrar, G. E., Jr.: The Dispensatory of the U.S.A., ed. 25, J. B. Lippincott, Phila., 1955, p. 1392. 2. Best, C. H. and Taylor, N. B.: The Physiologic Basis of Medical Practice, ed. 7, The Williams and Wilkins Co., Balt., 1961, p. 1104.

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references: (1) Nelson, W. E.: Textbook of Pediatrics, ed. 7, Philadelphia, W. B. Saunders Company, pp. 231-233, 1959. (2) Parrott, R. H., and Nelson, W. E.: *ibid.*, p. 759. (3) Johnston, J. A.: Ann. New York Acad. Sc. *69*:881-901 (Jan. 10) 1958. (4) Burke, B. S., and Kirkwood, S. B., in Greenhill, J. P.: Obstetrics, ed. 12, Philadelphia, W. B. Saunders Company, 1960, pp. 126-131. (5) Skillman, T. G.; Hamwi, G. J., and May, C.: Geriatrics *15*:464-472 (June) 1960.

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1. Smessaert, Andre, Collins, V. J., and Krocum, V. D.: *New York J. Med.* 55:1587, June 1, 1955.
2. Banyai, A. L.: *Geriatrics* 14:621, Oct., 1959

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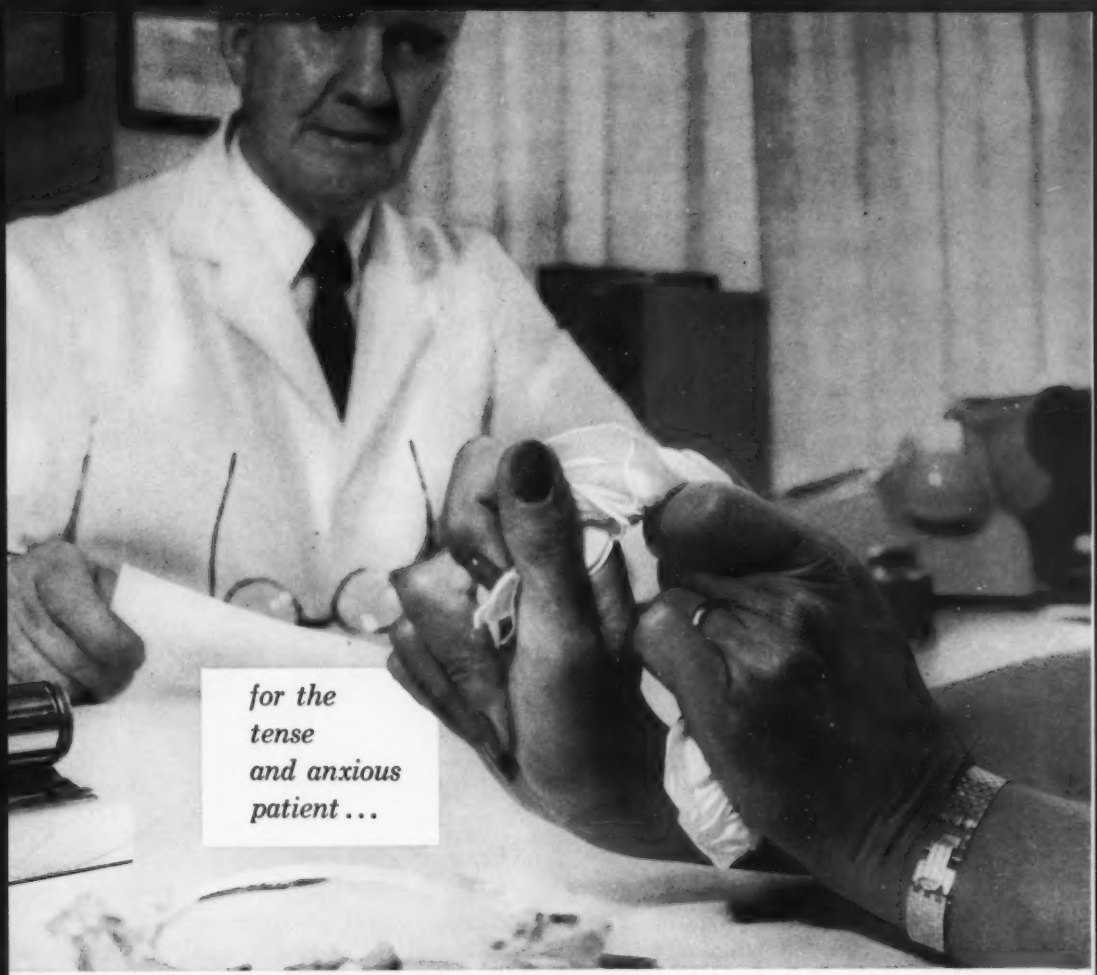

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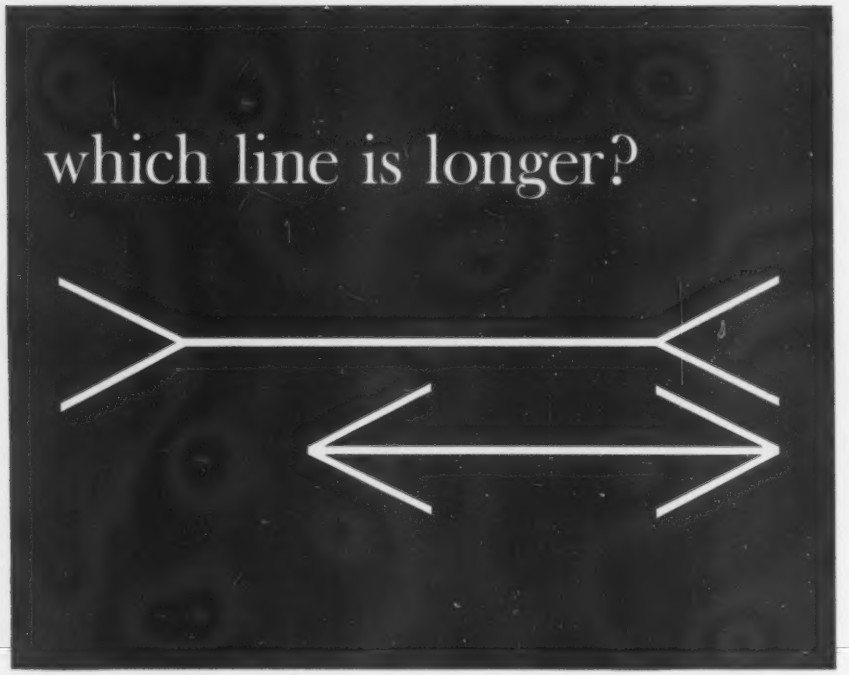

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1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:129, 1960.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 37, NO. 9 SEPTEMBER 1961

GENETICAL VARIATIONS IN THE SERUM PROTEINS OF MAN*

ALEXANDER G. BEARN

Associate Professor, The Rockefeller Institute, New York

IT would not be difficult to belabor the heaviness of the yoke under which the investigator in human genetics struggles, compared with his colleagues working with such malleable and docile creatures as drosophila, bacteria and neurospora. To be sure, in man, fine structure genetical analysis cannot yet be performed, but, perhaps for physiological genetics, man may have some advantages, for it is frequently feasible to make detailed biochemical studies on blood and other tissues which would be difficult or impossible in smaller organisms. In truth, of course, parochialism is dated. No one species is preferable to another for genetical study; each has its own special advantages and limitations.

The brilliant pioneering work of Beadle and Tatum, epitomized in the one gene, one enzyme concept, has resulted in a surge of interest in biochemical genetics for those working in human biology, for they disclosed simplicity under chaos and offered hope that nature's secrets were not always incomprehensibly complex. There is no doubt that the *fons et origo* of the expanding field of human biochemical genetics

* Presented at the Fourth Annual Postgraduate Week, *Frontiers in Medicine and Surgery*, of The New York Academy of Medicine, October 24, 1960.
These studies were supported by a Grant-in-Aid from the National Foundation.

today lies in their work, and in the perceptive genius of Archibald Garrod, distinguished son of a distinguished father, protégé of Bateson and of Hopkins, who first coined the term "inborn error of metabolism".

Although it is now generally agreed that genetic specificity resides in the base-pair sequences of DNA, the way this code conveys the information, via messenger RNA to the ribosomes where the proteins are synthesized, is less clear and will not be discussed further. Deductions concerning the genotype can only be made by recognition of various phenotypes. Moreover, the ability to recognize slight phenotypic differences in man will depend on the nature and precision of the tools employed. As long as human genetics was largely confined to quantitative polygenic traits such as body-build and intelligence, it was inevitable that precise information on the mechanism of gene action in man should be largely obscure.

Much of the recent progress in biochemical genetics in man stems from the development of techniques which enable the rapid separation of closely-related biochemical substances. Although their application has often been blind, the fruits have been surprisingly bountiful. The extensive use of paper chromatography to study urinary constituents has resulted in the disclosure of several hereditary amino-acidurias, and the application of electrophoresis to studies on the serum proteins has enabled these substances to be delineated and investigated in various populations.

Hereditary variations in the serum proteins can be considered from several viewpoints. The physician is most concerned with the relationship of these variations to disease and with the possibility that recognition of the abnormality will pave the way for rational and effective treatment. The biochemist and geneticist are convinced that the identification and characterization of the various mutant forms of the proteins, and a careful structural comparison of the products of the allelomorphic genes, will give considerable insight into the mechanism of gene action. The evolutionist, on his part, is interested in the reason for the existence of these variations and in the opportunity afforded by their existence for further progress in the biological evolution of mankind.

No longer content with the collection of exhaustive measurements of graded characteristics in different peoples, the modern anthropologist now leans heavily on the comparison of gene frequencies in different isolated populations in an attempt to delineate the existence and size

of isolates, and to determine the origins and movements of primitive groups. It is noteworthy in this connection that Livingstone,[1] in a recent study of the frequency of the sickle cell gene in Liberia, has suggested that selective factors are as important as gene flow or drift in establishing high frequencies of aberrant genes in at least one primitive population. A similar situation may explain the high frequency of Kuru, the severe and invariably lethal disease of the nervous system found exclusively in the Fore people in New Guinea.[2]

Variations in the serum proteins are frequently classified according to their electrophoretic mobility. However, I would prefer tonight to try to classify them according to the frequency of the genotype, a biological rather than a biochemical approach. It is important to recognize that, except for a few rare, clearly disadvantageous mutants, the belief that a common variant is *ipso facto* good or bad is meaningless. Evidence of a substantial and compelling nature indicates that the concept of a perfectly neutral gene is becoming increasingly untenable. It is to be anticipated, therefore, on theoretical grounds, that the various genotypes will exhibit different susceptibility to disease or will differ in relative fertility. But if we introduce the concept of balanced polymorphism, the next question inevitably becomes, what are the selective factors which keep the equilibrium balanced? Oversimplification is dangerous, for the superior fitness of the heterozygote may exist only under certain environmental conditions, and these conditions may no longer be present. A large intra-population store of genetic diversity is essential if man is to adapt to ecological change.

Common Variants

Common variants are defined in this context as those variants which exist in such proportion that they are unlikely to be maintained in the population by mutation pressure alone and thus are probably examples of balanced polymorphic systems. In practice, this means that if any trait exists in a population with a frequency greater than 5 per cent, a selective advantage for the carrier of the trait should be seriously considered. Fisher[3] pointed out, as long ago as 1930, that it is highly unlikely that neutral traits will be maintained in a population, but it is only within the past 15 years that the full implication of this work has become appreciated, largely through the writings of Ford, Dobzhansky and others.

It was rather more than 50 years after Landsteiner had described the heritable differences of human blood groups that suspicion was first raised that heritable differences in the serum proteins might exist in man. Recognition of heritable differences in the blood groups had to await the development of agglutination techniques. Heritable differences in the serum proteins, in their turn, had to await the development of refined electrophoretic techniques. In 1953, in a short and rather neglected paper, Bernfeld and his co-workers[4] described characteristic changes in the globulins of normal human serum which appeared unaltered by disease. In 1954 a study of the electrophoretic characteristics of the serum of normal mice revealed inherited differences in their serum proteins.[5] But it was clear that apart from gross abnormalities, the technique of paper electrophoresis was insufficiently sensitive to differentiate minor variations in the serum proteins. A better method was needed and was provided in 1955, when Smithies[6] devised a supporting gel of partially hydrolysed starch. Electrophoresis in this medium separated the proteins on the basis of absorption, size and shape as well as charge, and resulted in an electrophoretic pattern more complicated yet more illuminating.

Haptoglobin

In 1940 Jayle[7] identified an α^2 protein in human serum which had the unique property of binding hemoglobin. This substance was named haptoglobin and was thoroughly investigated chemically by the French workers. Indeed, in 1946 it became apparent that there were two types of haptoglobin which varied in their behavior when precipitated from serum using Cohn's fractionation procedure. However, it was not until 1955, as a result of the starch gel technique, that it became possible to establish that the haptoglobins were inherited as a two allele system with dominance.[8]

There were two unusual aspects of this genetical system. First, it appeared that the haptoglobin 1 allele directed the synthesis of a single protein, whereas the haptoglobin 2 allele appeared to synthesize several proteins. In addition, the pattern observed by mixing serum from the two homozygotes was not identical to the *in vivo* heterozygote. The first difficulty has been resolved by the observation that, if the gels are run under conditions which break the hydrogen and sulphydryl bonds, the haptoglobin 2 protein depolymerises and migrates as a single band.

Similar treatment to the haptoglobin 1 does not affect the electrophoretic pattern. A mixture of the two products in this case gives rise to the two expected bands. The product of the haptoglobin 2 gene is thus a monomer which in the cellular environment of the organism tends to form a stable polymeric series.[9]

The nature of the interaction between the products of the Hp^1 and Hp^2 genes in the cell which give rise to a distinct protein species in the heterozygote is not understood.[9a] The presence of this substance is of theoretical interest since, if the heterozygote possesses a biological advantage over the two homozygotes, the reason may reside in specific physiological properties characteristic of the product in the heterozygote. From the point of view of selection, it is the final cellular product, rather than the gene product, which matters.

The recognition that haptoglobin variants occurred in varying frequencies in certain populations followed the world-wide application of the starch gel technique. The commonest variant is haptoglobin type Hp 2-1 modified which, though superficially similar to type 2-1, differs in that, in the 2-1 mod, the first two haptoglobin bands are increased in concentration. The variant occurs almost exclusively in the Negro population, in which it occurs in a frequency of about 10 per cent. Reductive cleavage of the purified haptoglobins with mercaptoethanol and iodoacetamide revealed that the product of the haptoglobin 1 gene was identical with the usual 2-1, but the product of the Hp 2 gene was slightly different. Thus it seems likely that the mutation in the 2-1 mod variant occurs in the Hp 2 gene.[10]

Another haptoglobin variant, "Johnson" type, described by Giblett, and another described by Galatius-Jensen, will not be discussed in detail but are mentioned to indicate the increasing complexities of the haptoglobin problem. The presently recognized haptoglobin variants are illustrated in Figure 1.*

Haptoglobin was originally considered to be an invariable component of the serum proteins of man, but the observation that ahaptoglobinemia occurred in the presence of severe hemolytic anemia was understandable in view of the ability of haptoglobin to bind free hemoglobin. Of considerable interest was the report by Allison, Blumberg and Rees that, out of a series of 99 sera obtained from Nigerians, 33.6 per cent had no demonstrable haptoglobin. In Gambia, Harris found

* See footnote page 600.

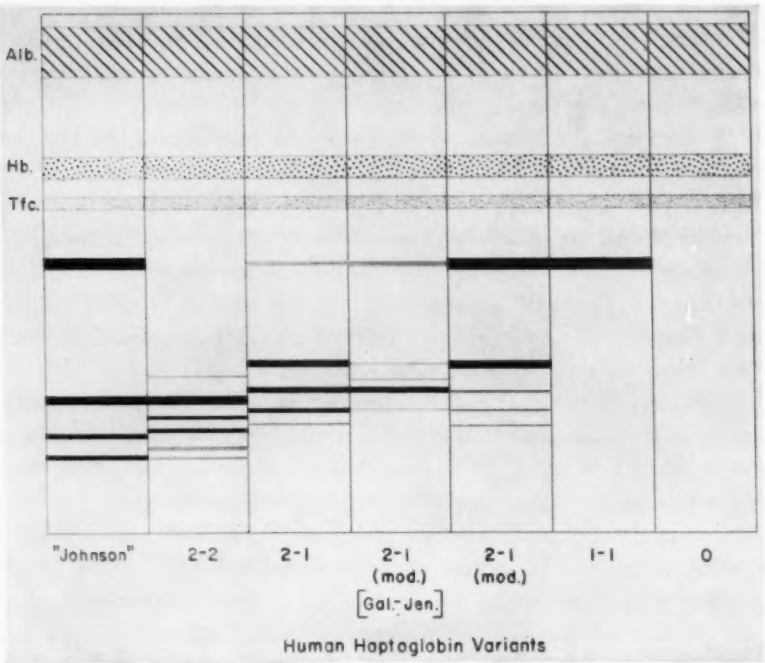

Fig. 1

about 40 per cent ahaptoglobinemia, and Allison and Barnicot have recently analyzed some tribes from East Africa and found a varying proportion of ahaptoglobinemia. This unusual type was considered a genetic variant and designated Hp O-O. A possible relationship between the incidence of ahaptoglobinemia and the incidence of malaria was immediately proposed.[11] Barnicot's data collected from northern Nigeria did not support his hypothesis.[12] However, the high frequency of ahaptoglobinemia in the Bagande and Bondei peoples of East Africa (24 per cent), a region where malaria is endemic compared with the low frequencies in Bushman, Zulu and Masai, who inhabit less malarious areas, suggests that this aspect should be pursued in greater detail.[13] Ahaptoglobinemia occurs in about 5 per cent of the Negro and may very rarely occur in the white population.

Sutton and co-workers suggested tentatively that the condition of ahaptoglobinemia could be explained on the basis of homozygosity for a recessive gene not at the haptoglobin locus. The observation that haptoglobin was occasionally clearly identifiable, in individuals classified as ahaptoglobinemia, was interpreted on the basis that the suppressor effect of the recessive gene was frequently incomplete.[14]

The investigation of Giblett and Steinberg sheds considerable light on the ahaptoglobinemia Hp O as well as the Hp 2-1 mod.[15] Their evidence suggests that both these phenotypes are in reality variants of Hp 2-1. The genetic explanation for the changed phenotype will require the analysis of further pedigrees. A modifier on the same or different chromosomes is a possibility, as is a separate allele at the haptoglobin locus, which, when heterozygous, could give rise to phenotypes 2-1, 2-1 mod or ahaptoglobinemia. The problem is essentially genetical and will be solved by the collection of more data.

The frequency of the haptoglobin 1 allele varies widely. In the American white the frequency is about 0.43, in the American Negro it is 0.59, and in the African Negro even higher, 0.72. The highest value so far recorded is 0.87 in the Yoruba tribe in Nigeria, and the lowest in an Indian group from Southeast Asia, where the frequency of the Hp 1 gene was 0.09. There are many points of interest in the haptoglobin distributions. The relatively low frequency of Hp^1 gene in the Athabascans of Alaska compared with the Apache (0.59)[16] and the Navajo Indians (0.44)[17] are noteworthy since both stem from the same linguistic stock. It will be of interest to compare the Hp^1 frequency in the Araucanian Indians of Chile, and these studies are under way. The differences observed may be due to selection rather than drift, though the nature of the selective factors is, as usual, obscure. It is interesting to reflect how rapidly information on haptoglobin frequencies throughout the world has been obtained, compared with the time needed to collect similar material on the blood groups.

Iron is transported in serum as a β_1 globulin which has been named transferrin, and, until the elaboration of the starch gel technique, it was assumed that everyone possessed the same transferrin. However, in the three years since the first variant was observed by Smithies,[18] an additional eight variants have been described. Analysis of pedigrees quickly disclosed that these variants were probably inherited as a multiple allelic series and were unassociated with disease. Unfortunately, however,

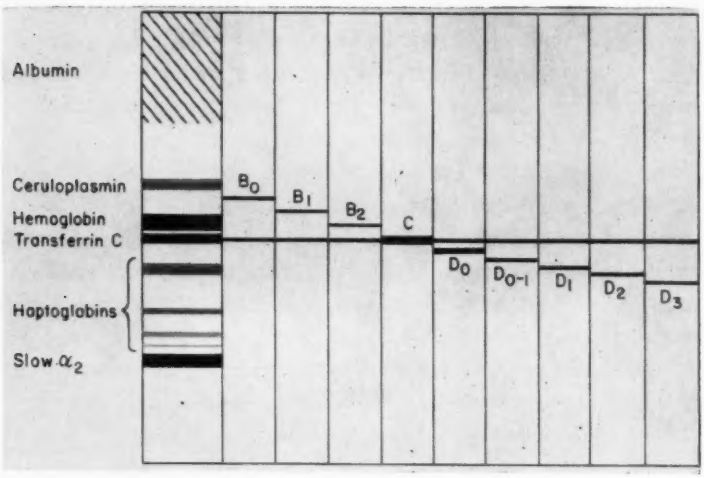

Fig. 2. Human Transferrin Variants

many of the variants are too rare to perform satisfactory family studies and we shall have to wait until families are found which contain more than two transferrins before we can investigate the possibility of several loci being involved. But the complex situation already demonstrated in sheep and cattle should make us cautious.

Population surveys have shown that the variants which electrophoretically migrate slower than transferrin C occur largely in Negroes and Australian aboriginies. These have been called transferrin D, whereas those which migrate faster than transferrin C have been called transferrin B. Variations have been observed within both groups and as a result of the work of several investigators the following transferrins have been recognized in man: B_0, B_1, B_2, C, D_0, D_{0-1}, D_1, D_2, D_3. The subscript refers to the relative mobility of the protein (Figure 2).* Gene frequency studies have lagged behind the recognition of these variants, partly because of their rarity, which depends on the particular type, but also because it is not easy, without reference sera, to be certain of the precise mobility of the transferrin and hence its classification. In

* Figures 1 and 2 are based on and similar to those published by Giblett, *Proc. Conf. Genetic Polymorphisms* (1960).

several laboratories, including our own, the addition of radioactive iron to the serum before electrophoresis is a routine procedure which simplifies the accurate positioning of the bands. Recently, in a joint project in association with Dr. Walsh McDermott and his colleagues from Cornell, we have been able to study the serum from 236 Navajo Indians from the point of view of transferrin variants. Parker,[17] in our laboratory, has observed an incidence of transferrin BC of 7.2 per cent, 95 per cent of which is one particular type B_1C. This incidence is greatly in excess of all previously reported values for other transferrins B.

One of the interesting aspects of the transferrin variants is that their number is so large that the difference in mobility cannot be accounted for by a single amino acid substitution in the polypeptide chain, unless certain substitutions substantially alter the pK of neighboring residues.[10] As with the haptoglobins, it seems likely that under some circumstances the abnormal transferrins confer an advantage and thus, on the average, the fitness of the heterozygote is greater than unity. The reason for the increased fitness is unclear. There is no doubt, as Haldane first emphasized, that ability to withstand infections would have been of immense selective advantage in the past. Interestingly, there is some preliminary evidence that the transferrin inhibits the multiplication of many common pathogenic viruses. In the presence of transferrin, viral synthesis can be reduced from 1/50 to 1/500 that of controls.[19] It seems a little unlikely that viral infections, except for smallpox, were as powerful selective forces in the past as bacterial infections. Nevertheless, resistance to a viral disease would also prevent the killing effects of secondary bacterial invaders. The demonstration of a specific advantage is frequently more convincing than to attempt to document a statistical heterozygous advantage.

Until four years ago no hereditary polymorphism was recognized in the gamma globulin. In 1956 Grubb found that if red cells, sensitized by incomplete Rh antibodies, were added to serum from certain patients with rheumatoid arthritis, they were agglutinated.[20] This agglutination could be inhibited by the sera of about 60 per cent of normal individuals. The inhibitor segregated in families, and it could be shown that these substances were controlled by a pair of allelomorphic genes called Gm and Gm^a, which gave rise to two phenotypes and three genotypes, Gm/Gm, Gm/Gm^a, Gm^a/Gm^a. The individuals who possessed one or more Gm^a genes were regarded as Gm (a+) inhibitors and those

Gm/Gm were Gm (a–) non-inhibitors. Last year Gm (a–) was identified by a specific serum and the present classification of the two major alleles is Gm^a and Gm^b.[21] In the same year a new factor Gm^x which appeared to be a third allele at this locus was found.[22] The system is rapidly becoming as complicated as the Rh system, and quite as interesting. The Gm system must ultimately emerge from an ingenious but devious serological reaction to be placed on the firm foundations of protein structure. With the widespread interest in the structure of gamma globulin we can look forward to an expanding field with profound genetical implications. Already other variants are being described: Steinberg's Gm-like (probably another allele) which occurs exclusively in Negroes, Gm^{ax} which occurs only in whites and Gm^r which, although commoner in Negroes, also occurs in whites.[23] Population surveys will be of the utmost interest, and despite the technical difficulties encountered in the testing system, information on the frequencies in various populations is accumulating more rapidly than it can be recorded.

Finally, I should like to discuss certain rare mutations which occur in man and are sometimes associated with, and sometimes actually cause, disease. Many variants have been described over the past few years but I shall confine myself to mentioning a few examples. In general, one might imagine that alteration in the base sequences of DNA would give rise to an equal number of phenotypes characterized, at the molecular level, by the synthesis of decreased amounts of a normal protein, or of normal (usually slightly decreased) amounts of a protein of different molecular constitution. In practice, it will be much more likely that the mutations causing a decreased synthesis will be detected more frequently than those which alter the structure of the protein. In the latter case the ease of destruction will be determined by the probability that a given mutation will alter the electrophoretic properties, heat, stability, or other easily-examined properties of the protein. Hidden mutations will necessarily be frequent.

It is thus not surprising that most of the rare mutant forms of the serum proteins have been of the quantitative rather than of the qualitative type. If the alteration in the amino acid sequence decreases the ease with which the protein can peel off the RNA template, then even the qualitatively-abnormal mutant protein will be formed in slightly decreased quantities.

Perhaps the most remarkable rare abnormality of the serum proteins described is the absence of serum albumin. This was first reported by Bennhold in 1954 and occurred in a brother and sister.[24] The functions of albumin are many. Preservation of the colloid osmotic pressure of the serum, transport of fatty acids and trace metals, are among the vital functions subserved by albumin. It was, therefore, extremely surprising when the sole symptom of those afflicted was slight dependent edema. It is of interest that infusions of serum albumin to one of the subjects showed that the half-life was twice as long as in normal subjects. Evidence for trace qualities of serum albumin in one of the patients, before any transfusions, has been obtained by Humphrey[25] and thus the condition is, as often occurs, a severe depression of the protein rather than a complete absence. The condition is probably recessively inherited since the parents were first cousins, but detailed genetical analysis has not been possible.

Another curious variation in the serum albumin was recognized by Knedel in 1957. In eight individuals from two families a double albumin peak was seen on paper electrophoresis.[26] The anomaly, which appears to be due to a single gene with complete manifestation, is unassociated with disease. The condition is not excessively rare, for at least 8 families with the double albumin peak have now been observed. A comparison of the structural differences of the two albumins will be greatly simplified if the number of peptides released by partial enzymatic digestion are not too numerous. In one family a peculiar dermatological condition was noted in father and son but other members of the family with the protein defect had no abnormality and it seems likely that the dermatological condition is a red herring.

Ceruloplasmin is the blue α_2 protein of serum first isolated by Holmberg and Laurell[27] and found to have a molecular weight of 181,000 and to contain 8 atoms of copper per molecule, 4 atoms of which have recently been shown to be more easily split off the protein than the remaining four.[28] A deficiency of the protein is one of the cardinal features of Wilson's disease. This disease is associated with widespread degeneration in the brain and basal ganglia and with cirrhosis of the liver. The disease usually has a fatal outcome in 5-15 years. Family studies have shown that the disease is inherited in an autosomal recessive fashion, with a large coefficient of inbreeding.[29]

Perhaps the principal chemical abnormality in this disease is an

increase in the total content of copper in the body and it has been very reasonably postulated[30] that ceruloplasmin may control the flux of copper from the external environment of the intestinal tract to the internal environment of the body. This hypothesis is weakened by a number of disturbing observations which have been amply recognized by the several investigators to whom this hypothesis remains attractive. There is a poor correlation between the level of this protein and the age of onset or severity of the disease. There are a few patients with the disease with normal levels of ceruloplasmin, and there are some patients with low levels of the protein who do not have the disease. Those who are reluctant to discard the primary role of ceruloplasmin emphasize the following facts. The depression of ceruloplasmin which occurs in some normal heterozygotes with the disease is very significant, though why they should not get the disease itself is not clear since the depression may be in the same range.

Perhaps we should be wary of too readily assuming that the ceruloplasmin found in normal amounts in some patients with Wilson's disease is structurally normal. The genetic material not only determines the amino acid sequences but also the rate of assembly of the amino acids into the final protein molecule. In the majority of cases the mutation might affect the rate of formation of the normal protein, whereas in the rare mutation the sequence may be altered, probably at a non-enzymatic site (since ceruloplasmin still functions as an oxidase), and a different protein is formed which superficially resembles ceruloplasmin. This is pure speculation and is useful only in that it emphasizes the need for structural studies on ceruloplasmin. Naturally, other explanations should not be excluded and perhaps the most likely is the elementary one that ceruloplasmin, although close to, is not the primary gene product. The conviction remains, however, that if the truly primary gene product can be recognized in the homozygote, it will be possible to detect the effect of the gene in the heterozygote in all instances, and further, that all the signs and symptoms of the disease will be strictly relatable to this primary change. Man, however, is a complex organism and it would be a mistake to believe that the effect of other genes at other loci, as well as environmental factors, did not play their role in the final picture. It may be that analysis of the problem of Wilson's disease, using tissue culture techniques, will prove useful in defining the differences between mutant and normal cells.

Agammaglobulinemia, although an inherited variation in the plasma proteins of great interest and significance, will not be discussed in detail since this disease, from a molecular point of view, is presently complicated. It is clear, in this instance, that gamma globulin is not the primary gene product. The primary effect of the abnormal x-linked gene is to prevent the normal development of plasma cells. One of the reflections of this abnormal development is a failure of the cell to produce its characteristic cellular products, the immunologically related substances collectively called the gamma globulins. There is little doubt that we are still on the threshold of discoveries in the field of inherited serum proteins and for their study all the methods and techniques of protein chemistry will need to be utilized.

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RELATION OF DEOXYRIBONUCLEIC ACID (DNA) TO VIRUS INFECTIONS AND TUMORS, WITH SPECIAL EMPHASIS ON THE SE POLYOMA VIRUS

(A Correlated Cytological, Histological and Cytochemical Study)*

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INTRODUCTION

ALTHOUGH it has been known for some years that infection with certain viruses will cause tumors in some animals, there is little information available as to the type of host-cell-virus relationship necessary for the transformation of normal cells to tumor cells; in short, the pathway by which these viruses produce tumors in the host is still obscure. Therefore, an exploration of the host-cell-virus relationship at various time periods seemed urgently needed, including those periods shortly after virus infection, that is, long before the tumor manifests itself.

A fruitful approach to this problem appeared to be offered by simultaneous cytopathological, histopathological and cytochemical studies, using light microscopy and microspectrophotometry. These techniques not only have the advantage that the host-cell-virus relationship can be examined in a large number of different cell types, required in establishing the steps in the sequence of virus-induced changes, but they also permit a direct comparison between morphological and chemical alterations of the same cell structure after viral infection.

One of the chemical components, in the host cell as well as in viruses, on which we have focused our special attention, is DNA. Our great interest in studying the quantitative behavior of DNA, and its relation to structural changes of cells and tissues in virus infections and

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tumors, has been stimulated by four major advances in our knowledge made within the last two decades:

1. DNA is an essential chemical building-stone of all nuclei, is constant in quantity and correlated to chromosomal complement in normal cells, and is a chemical component of genetic material.[1]
2. DNA is a chemical component of many viruses.[2]
3. DNA viruses may cause malignant tumors.[3]
4. DNA can be determined in single cells in microscopic sections *in situ* by Feulgen microspectrophotometry, a method which makes possible a direct correlation between morphology and DNA quantity of the same cell structure under the microscope.[4, 5]

a) The fact that DNA is not only of great significance for normal cell life, growth and genetic continuity, but that it is also an essential chemical building-stone of many viruses and that some of these DNA viruses may cause malignant tumors, would obviously make exploration of the interrelation between host cell DNA, virus DNA and tumor DNA a challenging problem.

b) It is also evident that, to answer specific questions such as: "What happens to the intracellular DNA content when a cell is infected with a DNA virus or when a normal cell becomes a tumor cell?", a method is needed, such as Feulgen microspectrophotometry, which permits simultaneous cytopathological and cytochemical studies of large numbers of cells in their natural environment.

Results

Among the various DNA viruses responsible for tumor formation, benign or malignant, such as molluscum contagiosum, verruca vulgaris, Shope papilloma, and polyoma, which we have investigated so far, we shall discuss here mainly our studies done in collaboration with Drs. Rudolf Leuchtenberger, S. E. Stewart and B. E. Eddy, which are concerned with the effect of polyoma virus on the mouse kidney.[6]

There are two main reasons for selecting this example:

1. SE polyoma virus is the first DNA virus known to produce a wide spectrum of malignant tumors in rodents.
2. The mouse kidney is a particularly favorable model for assessing the steps in the sequence of the polyoma-virus-induced changes.

TABLE I—ESSENTIAL MICROSCOPICAL FEATURES IN THE KIDNEYS OF MICE INFECTED AT BIRTH WITH POLYOMA VIRUS

Type of Tissue	*"Viral Activity"*						*"Cellular Activity"*			*Fate of Cells and Tissue*
	Striking Increase in Cellular and Nuclear Size	Intracytoplasmic and Intranuclear Ellipsoid Inclusions	Margination of Chromatin	Bursting of Cells	Expulsion of Spherical and Ellipsoid Inclusions	Cell and Tissue Necrosis	Mitosis	Hyperplasia	Abnormal Proliferation	
Epithelium of Convoluted Tubules	Present						Absent			Death
Stroma	Absent						Present			Tumor

TABLE II—DUAL EFFECT OF THE SAME VIRUS ON CELL MORPHOLOGY AND DNA CONTENT

Effect I				*Viral Infection*			*Effect II*			
Morphology			DNA Content				*Morphology*			DNA Content
Visible Intracell. Viral Activity	Mitosis	Fate of Cells	Increase in Intranuc. DNA	Designation of Virus	Host	Principal Viral Nucleic Acid	Visible Intracell. Viral Activity	Mitosis	Fate of Cells	Increase in Intranuc. DNA
Present	Absent	Death	Abnormally Large (Viral DNA?)	Adeno Type III, VII	Human	DNA	Absent	Present	Benign Prolif.	In Accord. with Mitosis
				Herpes Simplex					Benign Tumor	
				Verruca Vulgaris						
				Molluscum Contag.					Benign and Malig. Tumors	
				Shope	Mouse					
			Slight	Polyoma	Rabbit					

A. *Cytopathological and Histopathological Findings*

When newborn mice are infected with polyoma virus, the main cyto- and histopathological changes in the kidneys of the mice are found in the epithelium and in the stroma of the convoluted and collecting tubules, while the glomeruli revealed only minor alterations. As can be seen in Table I, the sequence of events and the type of lesion involving the epithelium of the convoluted tubules were strikingly different from the sequence and lesions occurring in the stroma of the kidney. The epithelium displays cellular features which may be designated as "viral activity", such as increase in cell size, inclusions, margination of chromatin, and absence of mitosis, resulting in death of cells, while the stroma does not reveal any of these steps, but, on the contrary, displays features which may be designated as "cellular activity", such as mitosis and proliferation, leading to tumor formation.

It should be pointed out that a study of the kidney at varying times after infection reveals that the "viral activity" in the epithelial cells precedes the proliferative activity of the stroma and that the stromal atypism increases with time. For example: early—that is, from 24 hours to approximately two weeks—after polyoma infection, only the epithelial cells of the convoluted tubules show significant alterations in the sequence as shown in this Table, while the stroma cells do not exhibit any change at this time. After this period, the stromal cells start to change in their own pattern; that is, they reveal a sequence of mitosis, hyperplasia and abnormal proliferation.

Characteristic examples of the sequence of events in the epithelial cells and in the stroma cells of the kidney after polyoma infection are given in Figures 1-4.

Figure 1, which illustrates the appearance of a kidney ten days after polyoma infection, reveals that some of the convoluted tubules disclose a striking increase in nuclear size associated with change in chromatin pattern and the occurrence of intracytoplasmic spherical inclusions. These inclusions contain DNA, as is evident when Feulgen reaction is carried out.

As can be seen in Figure 2, the increase in nuclear size is frequently followed by margination of chromatin, giving the nuclei an empty appearance: "ballooning". However, on careful cytological analysis, intranuclear ellipsoid inclusions can sometimes be discerned. These

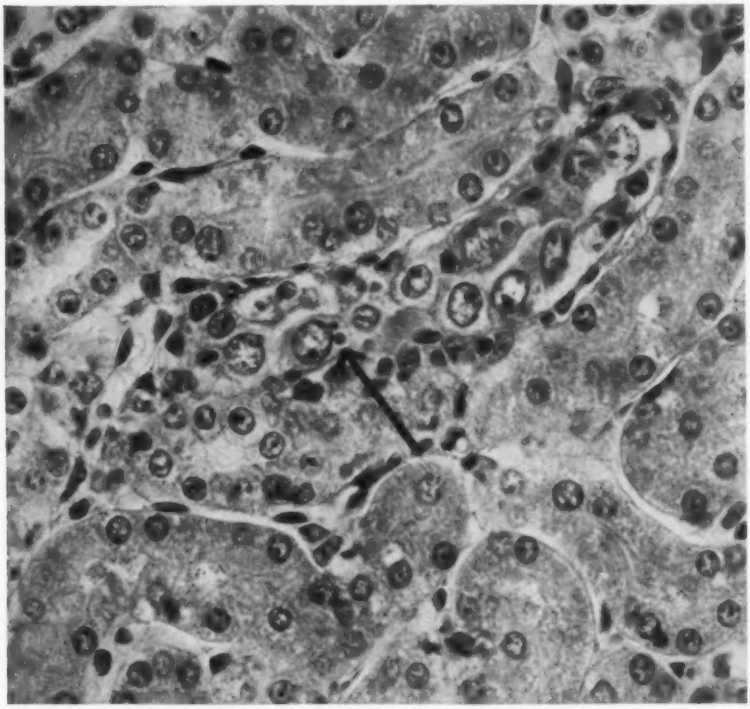

Fig. 1. Section of kidney of 10-day old mouse infected at birth with polyoma virus. Note, in the center, the abnormal appearance of epithelial cells lining the convoluted tubules, increase in nuclear size and intracytoplasmic *spherical* inclusions surrounded by halo (arrow). H. and E. X 600

intranuclear ellipsoid inclusions are particularly well seen in bursting nuclei, as illustrated in Figure 3, where epithelial cells seem just to release such particles from the nucleus. These inclusions contain only a small cap of DNA; the remainder is protein.

Considering now the changes in the stroma, which follow the epithelial alterations, a beginning hyperplasia of the stroma is frequently seen in the vicinity of tubular epithelial cells disclosing "viral activity". This proliferation gradually becomes more pronounced and associated with abnormalities, and may result in spindle cell sarcoma of the kidney, which will metastasize to other organs. The characteristic appearance of a kidney tumor is shown in Figure 4.

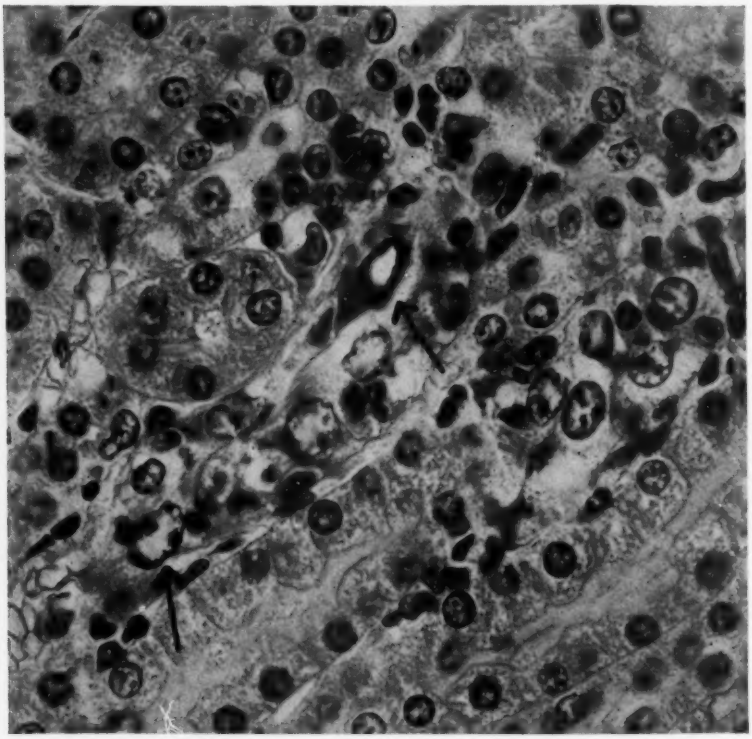

Fig. 2. Section of kidney of 17-day old mouse infected at birth with polyoma virus. Note different stages of necrosis of epithelial cells; margination of chromatin giving nuclei an empty appearance: "ballooned cells" (arrows). H. and E. X 900

B. *Cytochemical Findings—*DNA *Behavior In Cells*

Turning now to the cytochemical studies which were done simultaneously on the same material, with the purpose of assessing similarly the sequence of the DNA *changes*, the characteristic data, as obtained by Feulgen microspectrophotometry, are presented in Figure 5. If we examine first the DNA content in noninfected control cells, it can be seen that, in the nondividing cells of the kidney or any other tissue, the DNA content from cell to cell is indeed very constant, being 2DNA, corresponding to the characteristic diploid chromosomal complement; on the other hand, in dividing cells of the same kidney, there is an

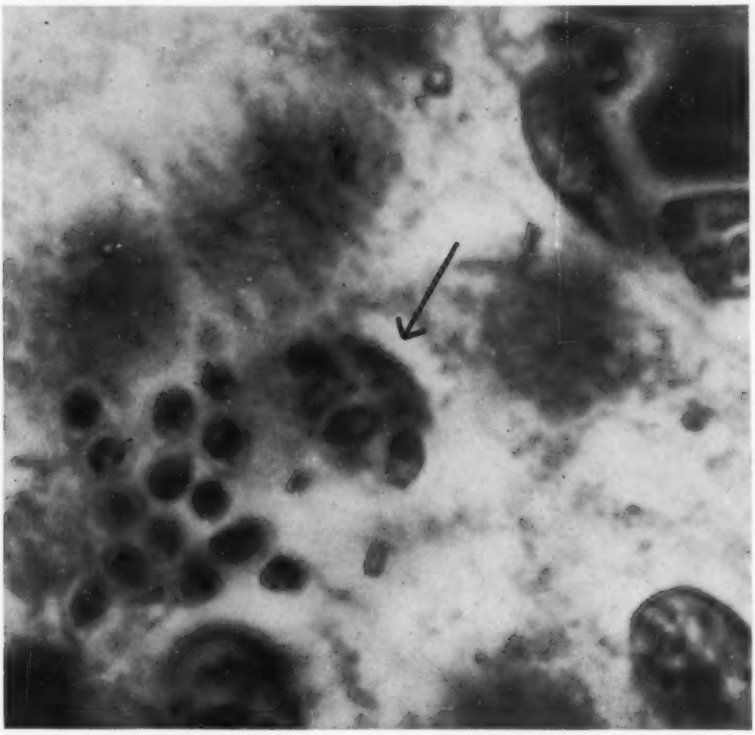

Fig. 3. Section of kidney of 17-day old mouse infected at birth with polyoma virus. Bursting of virus-infected epithelial cells and expulsion of numerous *ellipsoid* inclusions from nuclei. Observe the partly preserved nuclear membrane (arrow). Note also the small basophilic cap and the large amount of eosinophilic material in the ellipsoid inclusions. Observe fragments of glomerulus in upper right corner. H. and E. X approximately 3,000

increase from 2DNA to 4DNA, which is in accordance with DNA doubling required for the formation of two new daughter cells.

Now, if we look at the DNA values in polyoma-infected epithelial cells of the kidney, which reveal the visible "viral activity", it is evident that there is only a very slight increase of DNA over that of the non-infected control, and that the same holds true for the dividing stroma cells, when compared with dividing cells from controls. The similar DNA behavior in dividing normal and in dividing tumor cells after polyoma infection is in good accordance with other observations; namely,

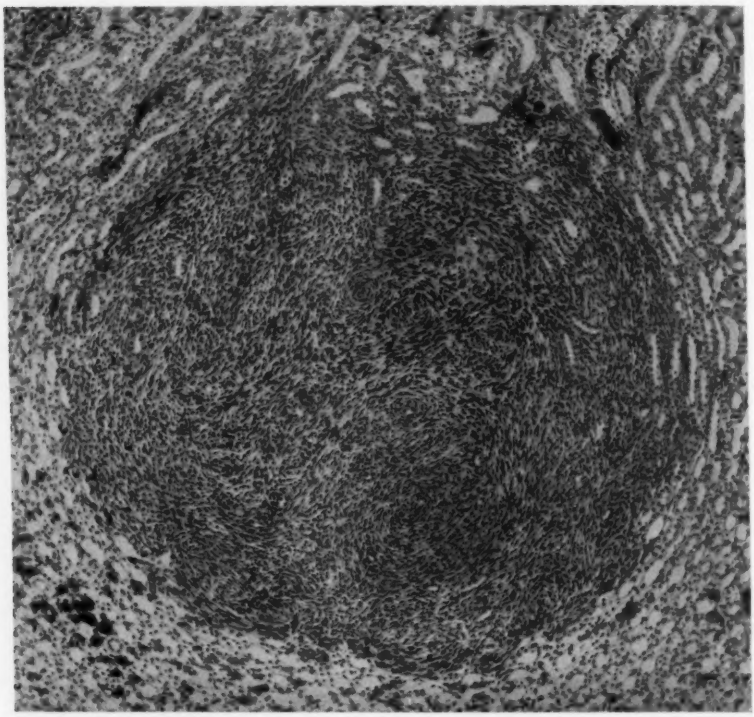

Fig. 4. Section of kidney of 5-week old mouse infected at birth with polyoma virus displaying tumor nodule (spindle cell sarcoma). H. and E. X 100

that any type of cell division is associated with DNA synthesis in the interphase nuclei. This increase in the DNA content is present regardless of whether the dividing tissue is a normal one, such as embryonic or regenerating tissue, or whether the dividing tissue is a tumorous one. On the other hand, the slight increase of the DNA content in the nondividing epithelial cells which show the "viral activity" after polyoma infection is indeed surprising, because all of the DNA viruses which we have studied so far have always evoked an abnormal augmentation of the DNA content in the nondividing cells showing visible "viral activity". One example chosen for comparison is that of verruca vulgaris, the common wart of the human. Here also, as in polyoma, there is a dual effect on the cells; some show visible "viral activity" leading to death,

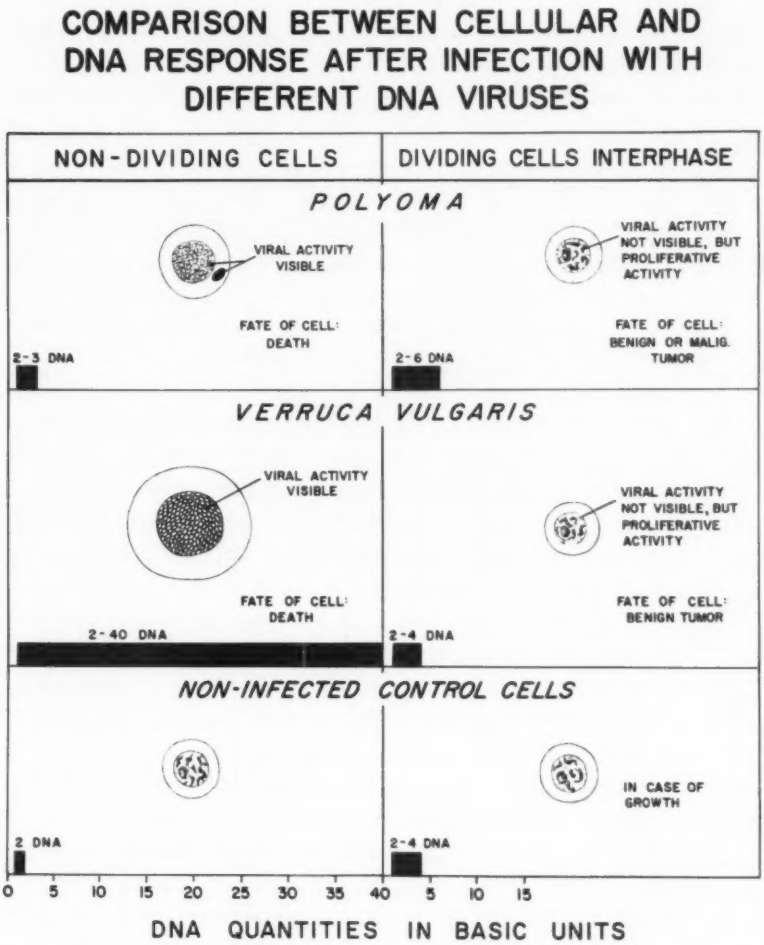
COMPARISON BETWEEN CELLULAR AND DNA RESPONSE AFTER INFECTION WITH DIFFERENT DNA VIRUSES
NON-DIVIDING CELLS
DIVIDING CELLS INTERPHASE
POLYOMA
VIRAL ACTIVITY VISIBLE
FATE OF CELL: DEATH
2-3 DNA
VIRAL ACTIVITY NOT VISIBLE, BUT PROLIFERATIVE ACTIVITY
FATE OF CELL: BENIGN OR MALIG. TUMOR
2-6 DNA
VERRUCA VULGARIS
VIRAL ACTIVITY VISIBLE
FATE OF CELL: DEATH
2-40 DNA
VIRAL ACTIVITY NOT VISIBLE, BUT PROLIFERATIVE ACTIVITY
FATE OF CELL: BENIGN TUMOR
2-4 DNA
NON-INFECTED CONTROL CELLS
2 DNA
IN CASE OF GROWTH
2-4 DNA
0 5 10 15 20 25 30 35 40 5 10 15
DNA QUANTITIES IN BASIC UNITS

Fig. 5. Comparison between cellular and DNA response after infection with different DNA viruses.

while others lack the "viral activity" but show proliferation. However, as can be seen here in these nondividing cells showing visible "viral activity", there is an abnormally high DNA content. Some cells reveal nearly twenty-fold increase in the DNA and a large scatter of DNA from cell to cell.

Perhaps the absence of such a striking intracellular DNA increase after polyoma infection may be explained by the possibility, as Bendich has suggested,[7] that polyoma virus may be a one-stranded DNA virus, as compared with the other DNA viruses, which seem to be two-stranded DNA.

Discussion of Results

On the basis of data presented so far, it thus appears that infection with polyoma virus evokes two strikingly different processes in the kidney:

(a) a *degenerative process* of the tubular epithelial cells associated with visible "viral activity" resulting in cell death;

(b) a *proliferative process* of the stroma cells associated with mitosis resulting in malignant tumors, whereby the degenerative process in the epithelium precedes the proliferative process in the stroma.

The elicitation of two opposite processes in tissue cells of the mouse kidney observed after polyoma infection is in good agreement with observations made on other tissues infected by other viruses. For example, Dawson[8] described destructive and proliferative lesions in the chicken chorioallantoic membrane after infection with herpes simplex, and, in our own studies with several DNA viruses, summarized in Table II, two different processes could be similarly observed.

As can be seen, quite a variety of DNA virus infections in different hosts, regardless of whether they are tumor viruses or infectious viruses, can produce such a double effect. It should be pointed out that the two opposite processes, although they were not seen simultaneously within the same cell, may occur in cells of the same tissue, as, for example, in the epithelium after verruca vulgaris. This certainly indicates that the kind of change evoked in a cell by a virus does not necessarily depend upon the cell origin.

The aspect which seems of much greater importance than the tissue type is the observation that, in the same host, the same DNA virus infection will evoke in some cells a host-cell-virus relationship which leads to cell death, and in other cells a host-cell-virus relationship which leads to cell proliferation and even malignant tumors. One may say that, in the one instance, designated here as Effect I, the virus becomes the master, because it uses the cell and its products for its own viral reduplication, suppressing cell multiplication and finally killing the cell. This

"viral activity" is also reflected in the altered DNA metabolism in cells after infection with DNA viruses, the only exception being the polyoma virus, which, in this respect, behaves like an RNA virus, in that it does not change significantly the intracellular DNA content. The abnormally large DNA content observed after infection with all of the other DNA viruses raises, of course, the question as to whether this DNA is multiplying viral DNA or is due to an abnormal synthesis of host cell DNA, induced by the presence of the DNA virus. Unfortunately, this question cannot be answered at present, particularly because we do not have methods available that permit a differentiation between intracellular virus DNA and host cell DNA *in situ*. However, if some speculation is permitted, we should like to say that it seems rather improbable that large quantities of DNA would be synthesized by cells that are about to die, because we know from all other instances in cell biology that cell death is usually preceded by a decrease of the basic DNA content, while DNA synthesis characteristically precedes cell multiplication. On the other hand, there are two features that lend support to the concept that the increase in DNA may be due to VIRAL DNA synthesis: One is that the bizarre DNA masses in the form of DNA inclusions, or even DNA crystals, which can be seen under the light microscope, appear under the electron microscope as aggregations of viral particles.[9] The other is the parallelism between the occurrence of these DNA masses and the increase in the viral titers, as assessed by serological and fluorescent antigen-antibody studies.

Turning now to Effect II, one may say that, in contrast to Effect I, the cell stays master, because here the cell uses the virus as a stimulus for its own cell reduplication, suppressing viral multiplication and resulting in a whole spectrum of proliferative changes, ranging from benign proliferation to benign and malignant tumors. Here the DNA content in the nuclei of proliferating cells does not show an unusual pattern but is increased in accordance with DNA synthesis during the mitotic process. Furthermore, it should be pointed out that, once the tumor manifests itself, no difference in cytopathology and DNA content can be detected between tumors caused by DNA or RNA viruses, tumors caused by known carcinogens (such as hydrocarbons) or tumors of unknown etiology, including human tumors.

While the material at our disposal did not permit time-sequential studies of all the virus infections tabulated here, in those cases where such studies were possible, as, for instance, after Shope papilloma,

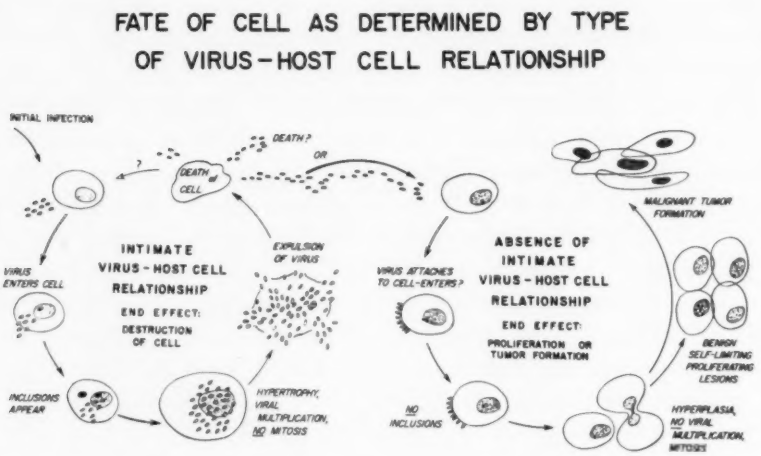

Fig. 6. Scheme of possible pathway of viruses within cells, resulting in death of some cells (first cycle), in proliferation and tumor formation of other cells (second cycle).

adenovirus, verruca vulgaris and polyoma, it appears that visible "viral activity" in nondividing cells and cell death do precede initiation of mitosis, proliferation and tumor formation of other cells.

Such a sequence, which can be particularly well demonstrated after polyoma infection in the kidney of mice, where, as has been shown, Effect I takes place in the epithelium and Effect II in the stroma, makes it reasonable to assume that both processes are interlinked; in other words, we should like to suggest that, after polyoma infection, tumor formation may be the result of two different host-cell-virus relationships in two cycles, as illustrated in the scheme in Figure 6.

The first cycle—designated as "visible intimate virus-host-cell relationship"—reveals, after infection with the virus, increase in cellular size, presence of inclusions, and other cellular changes consistent with viral activity, but no sign of cell division; instead, bursting of cells with release of viral particles occurs, finally resulting in death of cells. This cycle is followed by the second cycle, taking place in other cells. Here, after infection with the virus, the virus may also enter the cell, but its relationship to the host cell must be quite different, because no sign of visible "viral activity" can be observed. Instead, active cell division occurs, leading to proliferation of the tissue, resulting, after some viral

infections, such as verruca vulgaris and herpes simplex, in benign, self-limiting proliferation, or, after polyoma or Shope virus, in malignant tumor formation.

Whether the cycle of cell proliferation is initiated by exactly the same virus which evoked the cycle of intracellular "viral activity", or whether the virus may have changed after its activity in the nondividing cells, cannot be answered at present. Some support to the concept that, after polyoma infection, a changed virus or a cell viral product may be responsible for the abnormal cellular proliferation of the stroma may be derived from the observation that there are two types of "viral inclusions" after polyoma infection: 1) the cytoplasmic spherical inclusions, made up mainly of DNA and occurring very early after infection, when nuclear and cell membranes of the epithelial cells are still intact; and 2) the ellipsoid intranuclear inclusions, made up predominantly of protein and little DNA which are expelled from bursting epithelial cells just before stromal proliferation occurs.

That, after polyoma infection, the nondividing epithelial cells may contain the virus in the form of a whole infectious virus, while the proliferating tumor cells may contain the virus in the form of an incomplete virus, is also suggested by recent data of Sachs and Fogel.[10] These authors, who used fluorescent antigen-antibody technique, found that, after infection of mouse embryos with polyoma virus, the infected normal mouse cells exhibited fluorescence predominantly in the nuclei, while the tumor cells displayed the fluorescence in the cytoplasm. Noyes and Mellors[11] reported similar findings with the Shope papilloma, namely, that the virus could be detected only in the degenerating cells, but not in the proliferating ones.

These data and our own observation that, at least after infection with DNA viruses, viral reduplication and cell division apparently do not take place simultaneously in the same cell might explain why, in the past, the search for viruses in tumor cells has been so unrewarding. Such an exclusive relationship between cell division and viral multiplication would certainly suggest that nondividing cells displaying features associated with "viral activity" should provide a good source for isolation of tumor viruses, particularly when attempted at an early period after viral infection, while the tumor itself would be expected to be a poor source, yielding very little or no virus.

May we say in conclusion that we realize, of course, that our studies

cover only a very small aspect of the complex problem of the interrelationship between virus, host cell and tumor formation. Nevertheless, we hope that the finding of two different host-cell-virus relationships in this sequence, as assessed by combined morphological and quantitative cytochemical studies, may have stimulated an interest in pursuing further the problem of such dual effects of viruses and their implications for the process of tumor formation.

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THE PRESENT STATUS OF THE TREATMENT OF MÉNIÈRE'S DISEASE WITH ULTRASOUND*

FRANZ ALTMANN AND JULES G. WALTNER

IF, in the course of Ménière's disease, the vertiginous attacks become very severe and disabling for a long period of time and if they are not at all controlled by medical treatment, surgery should be contemplated.

Until recently the only reliable surgical methods consisted either of destructive labyrinthotomy or of intracranial section of the entire eighth nerve. The hearing is completely lost in both procedures while a high pitched, and occasionally very bothersome, ringing often persists.

Intracranial differential section of the vestibular portion of the eighth nerve (Dandy) preserves hearing at least for pure tones but is technically difficult. It is pointed out by Schuknecht that "preservation of pure auditory thresholds may not represent the preservation of usable hearing, for 75 per cent of the cochlear nerve fibers can be cut without creating a pure tone threshold loss. There is good evidence for suspecting that ears with a loss of neurone population suffer from a severe loss of auditory discrimination."

In view of the much greater dangers inherent in intracranial procedures, complete or partial section of the eighth nerve has been practically given up in favor of the destructive labyrinthine operations.

All attempts at preserving the cochlear function in direct interventions on the labyrinth have been unsuccessful (Altmann and Montreuil) and they are, therefore, only feasible in the relatively limited number of cases in which only one labyrinth is affected and in which the hearing on the diseased side has fallen permanently below the serviceable level. However, in view of the fact that involvement of the second labyrinth might occur three, four and more years after the first one,

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destruction of a hearing ear is always a somewhat risky procedure.

Chemical destruction of the vestibular endorgans by parenteral application of streptomycin has been shown to be possible (Fowler, Rüedi, Schuknecht and others) but has the disadvantage that the function of the healthy labyrinth is affected together with that of the diseased labyrinth.

Cervical sympathectomy has been recommended under the assumption that an autonomic imbalance resulting in paroxysmal labyrinthine vascular insufficiency is the cause of Ménière's disease; an attempt is made at eliminating or preventing the underlying vasomotor disorder (Passe, Seymour, Lewis, Wilmot and others).

Cervical sympathectomy seems to have a beneficial but often transistory effect upon the vertigo in about two-thirds of the cases and to a much lesser extent upon the tinnitus; the effect upon the hearing is variable. There are the usual unilateral nasal and Horner's syndrome complications.

Within the last few years a far more promising method has been developed by Arslan for selective destruction of the diseased vestibular portion of the labyrinth by means of radiation with ultrasonic waves.

Although attempts at treatment of the ear with ultrasonic waves date back for more than 30 years, the apparatus used at that time produced waves of such low intensity that they could not reach the inner ear at all. Later, machines capable of producing ultrasonic waves of higher frequency and of much higher intensity were used. It was shown in animal experiments that ultrasound produces first a stimulation of the vestibular apparatus but that application of larger doses, or of repeated stimuli, is followed by a complete loss of vestibular responses. Furthermore, it was demonstrated that in man even ultrasound of higher intensity, when applied to the outer surface of the mastoid, practically does not reach the inner ear because it is almost completely absorbed by air, and to a considerable extent by bone.

Histological studies on experimental animals showed that if the ultrasound actually reaches the entire inner ear not only the vestibular but also the cochlear portion is damaged.

Krejci, in other experiments, succeeded in selectively irradiating the vestibular portion of the inner ear by using a narrow beam of ultrasonic waves after operative exposure of the bony labyrinth; he actually eliminated the vestibular function but preserved the cochlear function.

He then successfully used the same procedure in a patient suffering from Ménière's disease. Arslan perfected Krejci's method by constructing, together with Federici, a thin and narrow sound wave transducer which produces a narrow beam of waves with a frequency of 800,000 to 1,000,000 c.p.s. and an intensity sufficient to produce a relatively rapid destruction of the vestibular portion of the inner ear on application to the bony wall of the lateral semicircular canal. Practically no ultrasound waves seem to reach the medial wall of the petrous bone and the posterior cranial fossa. Lateral transmission of ultrasound is prevented by special shielding and overheating is prevented by a cooling system.

Arslan reported excellent results in a large number of cases with disappearance of the vertiginous attacks in 95 per cent of his patients, with marked improvement in hearing in the lower and middle tonal range. The tinnitus improved in the majority of cases; in many it was completely eliminated.

The results reported by Arslan seemed so impressive that, after a visit to Arslan's department by one of us (J.G.W.), it was decided to try this treatment in the Ear, Nose and Throat Department of Presbyterian Hospital in New York.

The technique used by us in the series of cases to be reported in this paper followed the original technique employed by Arslan and was outlined by us in previous publications (Altmann and Waltner). The one major modification introduced by us is a thinning out of the prominence of the lateral semicircular canal with a polishing burr.

Premedication consists of secobarbital 100 mg. by mouth, two hours before operation and 100 mg. meperidine with 0.3 mg. atropin, subcutaneously one hour before operation.

The operation is carried out under local anesthesia with xylocaine 2 per cent with epinephrine 1:100,000. The mastoid is exposed through a retroauricular incision and entered. Enough cells are removed to get a good exposure of the antrum and of the prominence of the lateral semicircular canal; the incus remains undisturbed. In order to achieve a close contact between the tip of the soundhead and the lateral canal, the prominence of the latter is flattened out with a polishing burr under the operating microscope.

The tip of the soundhead is then applied to the lateral canal in such a way that the facial nerve and the cochlea are not included in the direct

path of the beam of ultrasonic waves.

Nystagmus starts, as a rule, one-half to one minute after the onset of the irradiation. The nystagmus must be constantly watched by an assistant, preferably with the help of Frenzel's glasses. At the same time the assistant looks for signs of irritation or paralysis of the facial nerve. If they should appear, the irradiation must be stopped immediately.

The initial nystagmus is "irritative" in type, with the quick component directed toward the treated side as with hot caloric stimulation. It lasts from 20-40 minutes, sometimes even longer. The homolateral nystagmus is followed by a short period without nystagmus and then frequently by a "paralytic" nystagmus directed to the not operated side. This nystagmus is most probably the result of severe damage to the sensory neuroepithelium of the cristae and maculae by the ultrasonic waves. The irradiation is then continued for another five minutes.

In order to get as complete a destruction as possible of the vestibular endorgans, the direction of the beam of the ultrasonic waves should also be directed to the other semicircular canals until no more "irritative" nystagmus can be produced in any position of the applicator.

In some patients, especially those with markedly reduced vestibular responses, the usual sequence of nystagmus is often absent; particularly, the contralateral "paralytic" nystagmus may not appear. The radiation is then continued for at least five minutes after disappearance of the homolateral nystagmus. If the homolateral nystagmus does not disappear, the radiation is continued for 55 to 60 minutes.

The intensity of the radiation depends on the intensity of the induced nystagmus. If the latter is marked with an intensity of 7 to 8 w/cm^2 on the dial of the machine, no further increase is necessary. If the nystagmus fails to appear at this intensity, it should be increased to 9 to 10 w/cm^2.

Higher intensities are rarely necessary and should be given with great caution. At the termination of the irradiation the wound is closed with mattress sutures.

The postoperative course is much less stormy than after surgical destruction of the labyrinth. There is little or no nausea or vomiting; the nystagmus disappears after 24 to 48 hours. Some but usually not very severe attacks of vertigo may occur during the first postoperative weeks; the unsteadiness after sudden movements of the head disappears completely after three to four months.

TABLE I—VERTIGO

AFTER THE FIRST RADIATION			AFTER A SECOND RADIATION IN 6 OF THE RECURRENT CASES	
Complete disappearance	30	57% } 76%	33	62% } 83%
Marked improvement (resumed normal work)	10	19% }	11	21% }
Recurrence	13	24%	9	17%
			53	
ANALYSIS OF THE 9 FAILURES				
Persistence of attacks after one radiation			3	
Persistence of attacks after two radiations			2	
Third radiation performed recently	1			
Labyrinthectomy	1			
Labyrinthectomy after first irradiation			1	
Bilateral hydrops with activity from the untreated labyrinth			3	
			9	
HEARING				
Improved			9	17%
Unchanged			35	71%
Worse			3	6%
Lost			3	6%
			50	
TINNITUS				
Disappeared			3	8%
Improved			11	29%
Unchanged			21	55%
Worse			3	8%
			38	

Among the patients operated between the beginning of June 1957 and the end of July 1960, there were 53 with a well established diagnosis of true Ménière's disease (endolymphatic hydrops) and a sufficient follow-up; 36 were males and 17 females. The results of the irradiation with regard to vertigo, hearing and tinnitus are shown in Table I.

The rate of completely successful primary operations is encouraging but not completely satisfactory. The main problem is the delivery of a

sufficient amount of ultrasound to the inner ear to bring about a complete and permanent elimination of the vestibular function. In a number of seemingly properly treated cases a return of the function was noted after several months and the return was often, but not always, accompanied by a return of the vertiginous attacks, while in others the labyrinthine responses had never been completely lost.

Analysis of the ultrasonic irradiation failures shows that at least three of them, and possibly four, still have a very good chance to be cured by a second or third irradiation. The same could have been the case with the patient who refused to undergo a second irradiation and chose surgical destruction of the labyrinth. Two of the three cases with bilateral labyrinthine involvement show markedly reduced hearing in both ears. In these cases we would rather consider treatment with streptomycin than radiation of the other ear because of the possible further hearing loss after radiation of the already severely damaged inner ear; in the third patient with relatively good hearing irradiation of the other labyrinth could be considered. In some cases of bilateral hydrops, for reasons not yet clearly understood, irradiation of one labyrinth seems sufficient.

In our patients we could not find any definite beneficial effect of the irradiation upon the hearing, as noted by Arslan, de Stefani and Bosotra in about one-fourth of their patients. We rather think that neither the improvement nor the deterioration noted in some of them exceeds the fluctuations frequently noted in Ménière's disease. Of the three cases with complete postoperative hearing loss, two had very little hearing left before the irradiation and in one the prominence of the lateral semicircular canal was thinned out until a "blue line" appeared; evidently too much ultrasound was delivered to the inner ear.

The results with regard to the ringing (cure or considerable improvement in 37 per cent of the patients), while not impressive, are better than those achieved with medical treatment and are not worse than the results from the methods of destructive surgical treatment. Among the three cases in whom the ringing became worse, one was a man of 71 years with marked cerebral arteriosclerosis and the deterioration was not necessarily the effect of the irradiation.

The only complication encountered was facial paralysis. It occurred in two cases in the course of the irradiation; a surgical decompression was performed a few days after the irradiation and the paralysis has

almost completely disappeared in one case after nine months, while in the other case it was still incomplete after ten months. In a third patient a facial paralysis developed seven days after the operation but disappeared completely after six weeks. In a recently operated patient, not included in this report, an incomplete paralysis developed after seven days and cleared up completely after three weeks under treatment with corticosteroids.

The facial paralysis occurring during operation is caused either by misdirecting the beam of ultrasound towards the facial nerve or, more frequently, by excessive heat developed in the tip of the applicator. The facial paralyses developing seven days after the operation are difficult to explain. Most probably they are caused by edema within the nerve in cases with dehiscences in the bony facial canal.

The results reported in this paper are not as good as those reported by Arslan but are similar to those of Dubs, Lumsden, Ironside and Lindsay, and Ariagno.

It is evident from an analysis of our own cases and of those reported by the other authors that undertreatment is practically the only cause for failure.

Remarkable progress in overcoming this difficulty has been made by Angell James and collaborators. They suggest certain technical improvements for the soundhead and stress the fact that the bony wall of the lateral semicircular canal must be thinned out as much as possible, at any rate to below a thickness of 1 mm., because a thickness of 1 mm. is "critical" and would permit only very little ultrasonic energy to enter the labyrinth. Angell James smoothes the prominence of the lateral semicircular canal with a diamond paste burr to a flat area through which the "blue" line can be seen very clearly. However, in view of the fact that in one case, where we thinned the bone over the prominence of the lateral semicircular canal that far down, the hearing was completely lost, we are somewhat hesitant to do it routinely. The soundhead is then applied under continuous irrigation of the operative cavity with physiological saline solution of body temperature. This ensures that the temperature does not rise above 44° C. during the operation and also provides complete transmission of the ultrasonic energy to the vestibular endorgans.

The last six patients, treated by Angell James after the efficiency of the apparatus had been improved, all obtained complete relief from

vertigo; the hearing was markedly improved in one case and slightly improved in two others.

Encouraged by these reports, we have used the irrigation method for the last three months and, judging from the results, we are quite satisfied with it. For continuous irrigation we use the attachment to the self-retaining retractor employed by Shambaugh in the fenestration operation. In an attempt to reduce the possibility of a facial paralysis developing several days after the operation, we now introduce a Penrose drain through the lower angle of the wound into the cavity and leave it there for two days.

It is to be hoped that with an improved soundhead and radiation under continuous irrigation the number of undertreated cases will decrease. Even at the present time radiation with ultrasound seems far superior to all other methods of surgical treatment and can be considered at a much earlier date than destructive labyrinthotomy. It can also be used in many patients in whom medical treatment seems the only possibility at present. The only group of patients in whom irradiation with ultrasound seems somewhat risky are those with bilateral hydrops and markedly depressed cochlear function. Here there is the possibility of a further hearing loss, a point also stressed by Angell James. In this group of patients treatment with streptomycin could be considered, provided they are below the age of 50 years.

Summary and Conclusions

The first therapeutic effort in Ménière's disease should always be medical.

A certain percentage of patients continue to suffer from crippling attacks of vertigo in spite of all kinds of medical treatment.

This latter group of patients can best be helped by selective ultrasonic destruction of the vestibular endorgans. This can be achieved by surgical exposure of the semicircular canals and by application of a narrow beam of high frequency and high intensity ultrasonic waves to the bony canal walls.

Ultrasonic surgery offers definite advantages over all other surgical treatments of Ménière's disease because the cochlear function is not destroyed. Irreversible, complete hearing loss is the rule in destructive labyrinthotomy. The results of cervical sympathectomy are far less satisfactory and often only transitory. Intracranial section of the eighth

nerve is technically difficult and not without danger to the patient's life.

Follow-up of 53 patients who underwent ultrasonic surgery revealed good results in 83 per cent of the cases. These patients resumed normal activities. With improved ultrasonic apparatus still better results are to be expected.

Ultrasonic surgery seems to have no definite beneficial effect upon the hearing. Thirty-seven per cent of the patients, however, reported complete cessation or definite improvement of tinnitus.

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USE OF STEROIDS IN RHEUMATIC DISEASES

*Transcription of a Panel Meeting**

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MODERATOR RAGAN: Our topic for this afternoon is "The Use of Steroids in Rheumatic Diseases", and it is of interest to recall that steroids have been used in this area only since 1949. In this period a great deal of material has been published, but there still remains a considerable difference of opinion as to the place of steroids in treatment, and I hope the members of the panel will discuss these many aspects. Indications for treatment vary from individual to individual and from place to place, both in the United States and abroad. In a few instances the contraindications are quite definite, but there are many exceptions.

In the time at our disposal it is impossible to discuss all rheumatic problems in which steroids have been advocated. We have, therefore, selected three major syndromes for consideration at this meeting: rheumatic fever, rheumatoid arthritis and systemic lupus.

In addition to the differences of opinion concerning the use of these steroids in clinical medicine, there are also wide differences of opinion with regard to their mechanism of action. The one which we favor is that there is suppression at the cellular level: some substance is not elaborated during the administration of adrenal 11-oxyglucocorticoids. This presumed substance is chemotactic for cells, and these cells do not invade under the influence of steroids. This modifies the inflammatory reaction, the repair, the growth and also modifies maintenance of structure, since cells do not last forever, and have to be replaced.

Another point of view is that in these diseases there is possibly a lack of adrenal hormones which are replaced by steroids in the same fashion that insulin replaces the lack of insulin in diabetes. However, there is little evidence for this, though there may be some hormone, so far not demonstrated, which may be playing a role in this situation. That is about as far as one can go in talking about mechanisms of action.

First, I should like to ask Dr. Fischel to discuss the use of steroids in the management of rheumatic fever.

DR. EDWARD E. FISCHEL: The use of steroids in rheumatic fever, as in other diseases, poses several questions: 1) what are the goals of management; 2) what are the variations in the course of the disease under consideration; and 3) what alternative types of management are available which may contribute to, or have advantages or disadvantages with regard to the objectives of management?

Until 1949 we had only salicylates and others of the so-called antipyretic agents, Phenacetin and aminopyrine, for use in the management

of rheumatic fever. There were many philosophies concerned with management which confused and beclouded the picture of what we were trying to accomplish in caring for patients with rheumatic fever.

The introduction of cortisone, perhaps more than any other single event, contributed to a serious appraisal, not only of the effect of cortisone and its related steroids, but to a reappraisal of all the antipyretic agents in the management of rheumatic fever. Similarly, of course, the previous experience contributed to the way people evaluated the use of the newer steroids in the treatment of this disease. This does not imply that the mechanism by which cortisone, or any of the other corticosteroids works, is the same or has the same common pathway as do salicylates. As far as I know, critical studies have consistently failed to determine a so-called definitive common pathway. As Dr. Ragan said, the exact mechanism of action of the steroids is still not clear; there is much to learn regarding the nature of the biochemical reaction that results in the anti-inflammatory and antipyretic effects of salicylates and related antipyretics.

With this inconclusive background the introduction of the steroids required a careful evaluation of all existing methods of therapy, including the newer ones. Advantage was taken of the fact that there were certain Centers that had agreed to participate in a cooperative study which was set up in a very searching and highly controlled fashion. The results of that study, at the end of one year, were published in *Circulation* in 1955. The results, at the end of three years, were presented at the International Congress of Rheumatic Diseases in Toronto, and the five year study is now in preparation.

In substance, while these agents perhaps act differently in time or on different manifestations of the acute disease, at the end of one and three years the relative incidence of heart disease in three groups studied, those treated with salicylates, those treated with ACTH, and those treated with cortisone, is the same. Those children who were admitted to the study with pre-existing heart disease, heart disease on admission, had a higher incidence of residual heart disease in the three groups. By and large, it is difficult to tell whether the steroids were better than, or the same as aspirin. The results appeared to be the same at that time, when residual cardiac damage was considered.

There have been many other studies in this field, some of them using higher dosages of steroids, but to date there is no well-controlled study

similar in design to the Cooperative Study. We find no data indicating any advantage for increased dosage of steroids, except that in some instances there is an obvious and impressive anti-inflammatory effect. If we achieve that—and, of course, that may be a major consideration in certain individual cases—I think we are doing everything possible for a patient. This, perhaps, would be one of the goals of management in the acute phase of the disease; namely, the suppression of any obvious signs of inflammation.

While the steroids are more dramatic in their effect on acute inflammatory reaction than salicylates, when one appraises the use of salicylates and their rather phenomenal effects, one does see anti-inflammatory activity which can not be disregarded.

Steroids are generally employed today in all instances where there is a manifestation of acute carditis. We are reluctant to employ them unless there is heart involvement, because the other manifestations of rheumatic fever are not as deleterious in the long run, and certain difficulties may be encountered with the use of steroids. These difficulties associated with the use of steroids indicate that they are not the final answer to therapy. First and foremost, steroids have occasionally been used in conditions which have not been well diagnosed. These include febrile conditions, or conditions associated with arthralgia, where a bacterial agent may be responsible for the disease; e.g., gonococcal joint, tuberculosis, subacute bacterial endocarditis, even perinephric abscess, have been mistakenly treated with steroids as rheumatic disease, and to the disadvantage of the patient. Not only does this delay proper therapy, but it may actually cause more severe tissue damage than might have occurred without steroids. A second shortcoming would be the toxicity resulting from long continued use, which will be discussed by the other members of the panel.

Finally, a manifestation that arises from the use of steroids and perhaps to a lesser degree with salicylates, is the occurrence of a rebound, when the drug is discontinued. The rebound can be very disconcerting. It may be considerably more than the mild flareup that is usually seen. It may be severe enough to precipitate cardiac failure, or even death, in a few isolated instances. It is something to be avoided, but when seen it can provide a lesson which suggests that it is better to avoid this kind of renewed inflammatory reaction. There is no proof that the inflammatory reaction *per se* causes accelerated valve disease, but the prob-

ability is suggested. With that in mind, we have developed a regimen of combined therapy using the advantages of steroids for rapid suppression of inflammation, and the advantages of salicylate for its long continued suppression. We are not sure that we are doing much better with this regime than with either drug alone, but there seems to be some basis in the pathogenesis of this inflammatory recation that suggests that an advantage may be obtained. It is difficult to have controlled studies—and we don't claim to have them for this recommendation—but with combined therapy, using both drugs to their maximum advantage, we believe we are getting somewhat closer to one of the desiderata in therapy of this disease.

Certainly, there has been insufficent experience in dealing with rheumatic fever with anything but the prednisone, prednisolone derivates, and before that with hydrocortisone and cortisone itself, to warrant a statement as to any relative efficacy. This has just been an attempt to point out our approach, how we estimate what may be achieved and how we try to achieve it.

One other recent and relatively new approach has been introduced into this field and discussed in an article in the *New England Journal of Medicine*. Dr. Rammelkamp and his colleagues presented evidence, perhaps not adequate, which states that penicillin itself may have a curative effect in acute rheumatic fever. I raise this issue, not because of the *pros* or *cons* of the regimen used, but because of the premise on which it is based; namely, the persistence of streptococci in the heart tissue. Were this established it might preclude or contraindicate the use of agents such as corticosteroids. Penicillin is used in the course of rheumatic fever, but we base our use of it on other more firmly established criteria of efficacy, such as prophylaxis in the prevention of recurrent infection. Those are the chief points I wished to make.

MODERATOR RAGAN: I have asked Dr. Bayles to discuss the use of steroids in rheumatoid arthritis.

DR. THEODORE BAYLES: Dr. Fischel had an easy assignment: a nice self-limited disease running for two, three, or six months; treat with steroids, the patient improves, and then it is all over. Those of us who deal with rheumatoid arthritis have a bear of a different size by the tail. As you well know from your own practices, this is a chronic disease which is not self-limited. Dr. Bauer's lugubrious statement, "once an arthritic always an arthritic", is probably pretty close to the truth, and

one takes on a long, difficult problem when one starts to use, in a disease of this nature, any compound in physiologically excessive dosage over a long period of time. Ten years ago we first used ACTH and it all seemed very wonderful to find that it suppressed the signs and symptoms of the disease and of the inflammation, that patients felt better, that it improved their nutrition, elevated their mood, improved their anemia, and seemed to block a great many of the undesirable features of the disease. However, this honeymoon did not last very long, and we were soon aware of the many problems that have beset all of us since then. It has been referred to—properly, I think—as a two-edged sword, and I shall try to show you both sides of the sword today.

Dr. Freyberg will discuss later the first problem that arises in long-term steroid therapy, that of the obvious sodium and water retention—observed in the first days of ACTH and cortisone—which has been overcome with the new compounds that he will discuss. The problem of potassium loss, of course, can be corrected by increasing potassium intake, and consequently does not present a real problem in the handling of the long-term patient.

The effects of the corticosteroids on the over-all protein metabolism were negative nitrogen balance, osteoporosis, and muscle wasting and other changes seen in association with these compounds. It is certainly one of the most discouraging parts of the picture in treating a chronic disease. High protein diets, large amounts of estrogens, and possibly even androgens, can perhaps improve such conditions; but no one has conclusively shown that these ill effects can be completely counteracted. The problem of peptic ulcer occurs in the chronic disease. With prolonged treatment of the chronic disease we now know that there is an increase in uropepsin. What this has to do with the formation of ulcers is not too clear.

Of a series of patients treated with prednisone 16 per cent had ulcers. Dr. Walter Bauer's control series on aspirin, which may be mildly but not highly ulcerogenic, was 8 per cent, so we know there seem to be increasing problems with peptic ulceration in the use of steroids in chronic disease. As Dr. Fischel has reminded us, we have all seen patients who have had overwhelming infections in the course of steroid treatment. Their protective mechanisms, mentioned by Dr. Ragan, are probably impaired during this period of Cushing's disease.

As to mental disturbances, while elevation of mood is a good thing

in all patients, certainly the severe depressions, the psychoses and other forms of mental aberrations which we have seen in patients with rheumatoid arthritis receiving steroids, are rather discouraging to the physician. Although everyone does not agree, my personal opinion is that a definite relationship exists between the dose and the duration of treatment and the incidence of mental disturbances, including the underlying psychologic background of the patient.

The diabetogenic aspects of steroids, I believe, have not been too serious a problem, but diabetes mellitus is usually accelerated or made worse and certainly presents a difficult problem in chronic disease.

Adrenal suppression is a real problem, the long-term effects of which are not yet known and which have not been adequately studied. We have treated a group of patients for short periods of time with the dosages of 500 mg. of cortisone per day for 14 to 28 days, with the adrenal response apparently returning to normal in about two to four weeks, in this group. However, any practitioner who maintains a patient on steroids must think in terms of the dire effects upon the patient should there be a sudden infectious or traumatic assault such as lobar pneumonia, accident, shock or surgery. Since there are known instances of patients on steroid therapy who have died of lobar pneumonia, it is of utmost importance to the patient that the physician proceed with the greatest caution when treating with a steroid. We personally meet this problem by giving 100 mg. of hydrocortisone intravenously on the day of operation, following that, on the first postoperative day, by giving 200 mg. by mouth, if possible, and tapering off during the next five to seven days.

In this particular situation, ACTH has no place, because the adrenal is not responsive nor will it respond.

The problem of pituitary suppression is not answered, since it has never really been measured. An interesting physiologic trick has been made possible by using a Ciba drug, SU4885. When this drug is administered, the pituitary response can be evaluated in terms of ACTH output. Under the influence of this drug the adrenal puts out Compound S rather than Compound F; therefore, the pituitary supposedly recognizes a physiologic need and puts out large amounts of ACTH. So far, in studies made upon our patients who have been on steroids—some of them for years—the ACTH response to SU4885 is quite normal; in fact, higher than in some of the normal individuals. Certainly, measurable

amounts of ACTH appear, but as to the long-term effects on the pituitary, the answer is not known. There are changes in Crooke's cells and other areas of the anterior pituitary that may be the results of long-term steroid therapy.

To regress from the pituitary to the seat of the soul, the hypothalamus, no one knows anything about the humoral substances that affect the pituitary.

Again, there is another problem associated with long-term steroid therapy, described by Dr. Slocumb at the Mayo Clinic, so-called hypercortisonism. This usually appears in patients who have prolonged high-dosage treatment with steroids. The dose is increased with no beneficial results. Finally, in desperation, the physician reduces the steroid dosage. The patient becomes depressed, febrile, severely ill, with muscle aches and pains, abdominal pain, and presents a very difficult situation. No one can be sure what this state of affairs really represents. It is almost like withdrawal of morphine, and has been compared to an addiction-like physiologic situation. In our own experience with the hypercortisone syndrome we have changed to hydrocortisone from the synthetic analogues and given heavy dosages of salicylates, and it has taken weeks to stabilize the patient with this clinical problem.

Vasculitis is probably related to this, although we are not sure. Dr. Kulka of our institution has been particularly interested in this problem, and has demonstrated its occurrence in rheumatoid arthritis. Interestingly enough, the earliest lesions are in the venules rather than the arterioles. Associated vasculitis can be found in practically every patient with rheumatoid arthritis and, usually, a round-cell infiltration and a rather mild form of inflammatory response, in patients who have not been on steroids. In the arteritis of patients who have been on steroids there is a marked difference, with a polymorphonuclear infiltration of vessel wall, almost necrotic-looking or acutely inflamed in appearance. Dr. Kulka, who is an experienced pathologist in this field, has seen this microscopic picture only rarely in patients with rheumatoid arthritis who have not had steroids; in fact, on occasion, the pathologist when confronted with this situation, has questioned whether the patient did not have an overwhelming sepsis. This was not the case, however, in the patient who showed the polymorphonuclear infiltration and acute vasculitis type of reaction which we have only seen when steroids were given.

It is quite apparent that we take a rather dim view of giving these compounds in managing chronic disease, but this does not gainsay their proper use, nor does it mean that drugs of this kind are not at times most helpful in treating chronic inflammatory disease. I think their use is limited, and I shall try to outline some of my own thoughts about them. As I said, Dr. Fischel has the nicest problem: he just suppresses inflammation and then everything is all right, but our problem arises from our inability to look forward to the disappearance of the disease within a reasonable length of time and, therefore, we are faced with the possibility that these patients may develop Cushing's disease. Dr. Ragan and one of his associates has pointed out, in an excellent review, that untreated Cushing's disease is invariably fatal. Therefore, when large doses are administered with what might seem, initially, to be very good effects, we may, in fact, be responsible for producing a fatal pathologic situation.

Another approach is what I have termed "aspirinoid" (which is a very bad word, a combination of a trade name and a Greek suffix), which describes procedures now used at the Mayo Clinic, in giving extremely low doses of steroids to produce an anti-inflammatory effect without inducing Cushing's disease. This is probably the practice now most frequently followed in dealing with rheumatoid arthritis. Before continuing, I should say that I agree with Dr. Fischel's position that every patient with rheumatoid arthritis should be on salicylates regardless of whether steroids are given or not. The amount of steroids given can then be reduced. A program of rest, physiotherapy and all the regimens which apply to a patient with a difficult chronic disease should be instituted.

I know of only one study of any significance with a control series in rheumatoid arthritis. An English clinic had two groups of patients with early rheumatoid arthritis. One group received aspirin and the other group cortisone. Rheumatoid arthritis progressed in both groups, and to the same degree, despite the use of cortisone in one group. However, one factor must be remembered: any damaged joint will show progression, by x-ray or by physical examination, even if the disease subsides, so that some of the measurements of progression of rheumatoid arthritis are difficult to evaluate. Nevertheless, I would agree with the conclusion of the English group, that the disease progresses as much when treated with cortisone as with aspirin. They stated, how-

ever (and we would agree), that some patients preferred cortisone because of its greater anti-inflammatory effect. There is no question in my mind that cortisone is more antiphlogistic than aspirin. We now come to the way in which we use the corticosteroids, which you will see is limited: patients with high fever, weight loss, running a downhill course, for whom all other available means have been used and have not had any effect. These would indicate situations in which small amounts of steroids should be used. However, to mention our own results at the Robert Breck Brigham Hospital, we have had unhappy experiences in treating with steroids those very sick children with Still's disease, usually a rather fulminant form of rheumatoid arthritis. We have been unable to discontinue the medication. They have developed amyloidosis, a possibility in any circumstance, but it seemed to be accelerated. One child developed hypertension, hypertensive encephalopathy, and ended up with very limited intelligence. Other patients developed infections, and altogether the treatment of acutely ill children with steroids has not produced satisfactory results.

In practicing the art of medicine, there is an economic aspect involved in the use of steroids. A patient with a long-term chronic disease, such as rheumatoid arthritis, must, if possible, remain at work and must assume responsibility for the support of his family. Is it wise to give steroids in these circumstances? After everything else has been tried, I think one is then probably justified in using steroids cautiously. We do use them during rehabilitation. A patient who has not walked for a year or two may be admitted to the hospital, and we give steroids for two to four weeks during the period of intensive hospital care and rehabilitation, to aid him to get back on his feet, use crutches, and do other helpful things. This is not given on a continuing basis, but once the patient gets going, so to say, he can often continue to keep active after this period of rehabilitation.

What are the contraindications? I think they vary a great deal with the individual patient. Obviously, pulmonary tuberculosis, a history of peptic ulcer, hemorrhage from peptic ulcer, mental aberrations, nervous breakdowns in the past are, to my mind, sufficient reasons to be hesitant in initiating steroid therapy, except as a last resort. A final contraindication, in our experience, is psoriasis. At the Robert Breck Brigham Hospital we have treated 30 patients for generalized psoriasis. Sixteen of these patients did not receive steroids. One of the 16 developed a

severe exfoliative generalized spread of this skin disease. Of the 14 patients who received steroids, eight had severe generalized skin reactions, six of these were of the exfoliative type, which impels us to include generalized psoriasis as a contraindication to steroid treatment in rheumatoid arthritis.

To conclude, we prefer the use of "aspirinoid" doses of steroids for short periods of time, in certain situations which fail to respond to normal dosage.

MODERATOR RAGAN: I think it is only fair to say that I disagree heartily with Dr. Bayles in certain of his statements. Dr. Freyberg will probably disagree with both of us. This is the situation at the present time, and I don't think we can wait for the question and answer period to make these disagreements known.

I shall say a few words about systemic lupus and the use of steroids in this syndrome. This is a disease which is apparently now being seen somewhat more frequently than formerly. This may be related to the current interest in steroids, the fact that something can be done for the patient, and secondly, to the fact that the LE preparation is now available. Many patients who were previously diagnosed otherwise are now considered to have systemic lupus.

Despite the fact that I disagree with Dr. Bayles on some points, in general I agree that one should be very hesitant in using steroids in rheumatoid arthritis. In lupus, this is not the case, primarily because we are faced with a potentially fatal disease in many instances. The second point is that we have become aware that this disease frequently is episodic and if a patient can be carried through an episode, one's efforts with the use of steroids may well be lifesaving. This does not mean that every patient with systemic lupus should be on steroids. A valiant effort should be made to control with other methods before becoming involved with this type of therapy. Our patients are started on salicylates. By and large, we carry them by treating the front sheet of the patient's chart, e.g., we try to suppress fever and tachycardia. This may require doses somewhat astronomical in amount, and throughout the literature some of the doses recommended are much greater than those we use. Doses of a gram of cortisone per day have been advocated. We believe that we get into trouble with such high doses and seldom give more than 200 mg. of prednisone daily. If it is borne in mind that one is dealing with a potentially fatal disease, which may be episodic, these

extremes are justified.

Just as an aside, we see less peptic ulcer in patients with systemic lupus than in those with rheumatoid arthritis treated with steroids. We have had one patient who died from a perforated ulcer who had systemic lupus without joint symptoms.

I would like to review the various parameters of patients with systemic lupus to give our point of view of the management. With regard to fever, we believe it must be suppressed. One point must be kept in mind when the patient comes in with a new fever while on doses of steroids which are moderately elevated. One must decide whether one is dealing with an exacerbation of disease or with a recurrent infection. When this was not kept in mind, some unfortunate experiences resulted. These patients are acutely ill. As has been mentioned several times before, they handle infections badly, and infection can become violently flamboyant and widespread. We increase the dose of steroids as well as administer bactericidal antibiotics. We prefer penicillin and streptomycin, after the proper cultures have been obtained. When the cultures are reported and we know where we stand, then the appropriate antibiotics can be given. We have had patients who died because a bacteriostatic antibiotic (such as one of the broad spectrum mycins) was used, one was a case of fulminating pneumococcal infection. It is safest to use bactericidal antibiotics until the exact organism has been determined, since patients on large doses of steroids do not present the usual signs and symptoms.

In our postmortem series of lupus, the large majority of deaths has been associated with overwhelming sepsis.

Two aspects must be considered in dealing with the renal area. One is renal insufficiency with azotemia, and the other is the nephrotic syndrome. This distinction is not too well defined. Kark, Pirani, Montgomery and their group, using serial renal biopsies, have been able to show that once renal involvement has appeared, the amount of steroids given has not modified the renal picture. In contradistinction to this, we have, on three or four occasions, seen patients with marked azotemia who seem to have reverted and cleared their azotemia for a period of a year or more. Most of our experiences are comparable to those of Kark and his associates in that, regardless of the amount of steroids given, when a patient develops azotemia it is terminal; but there have been enough exceptional instances to warrant its continued use. Two instances

have been reported where there has been a conversion from azotemia to a normal BUN. In such a situation we are inclined to increase the dose of steroids as a desperate measure.

Regarding nephrosis, using a moderate dose of steroids, 30 to 50 mg. per day has not convinced us that we have been able to modify the nephrotic picture in lupus. True, diuresis has resulted, but in no instance has the protein disappeared from the urine. Holman, at the Rockefeller Institute, using 80 to 100 mg. of prednisone per day for periods as long as six months, has had complete reversion to normal. We have seldom been able to keep any patient on steroids this long without something untoward developing.

As far as seizures go, which are not uncommon in systemic lupus, we believe steroids should not be withdrawn during the presence of seizures. This is probably a manifestation of organic vascular change, which also applies in the psychoses. This is in direct contradistinction to the psychoses seen during the use of steroids in rheumatoid arthritis. In lupus we believe there is supporting evidence to show that the steroids should be continued during the psychosis, that in most instances the psychoses are of an organic kind, and that withdrawal of steroids does not benefit them to any extent. Accordingly, our practice is to continue the steroids and treat the psychosis in the usual fashion. If restraint therapy is indicated, we use it; if medicinal therapy is indicated, we proceed with it, but maintain the steroids at a certain level, and do not necessarily increase them during the psychosis. These psychotic episodes may be short-lived. This disease is most episodic. One heartening thing that can be told the family is that the present episode may subside.

The typical joint involvement of rheumatoid arthritis can be seen in a patient with systemic lupus. There have been a reasonable number of reports of the most specific lesion in rheumatoid arthritis—the nodule—appearing in a patient who had lupus at post-mortem. In these situations we prefer the "aspirinoid" treatment of joints, because the process in the joints is not lethal, and we do not like to use large doses of steroids to suppress joint symptoms alone. The joint may sometimes be as full-blown and long-lasting as in typical rheumatoid arthritis.

With regard to withdrawal of steroids, the same phenomenon occurs as in Dr. Fischel's rebound and in Dr. Bayles' adrenal insufficiency. We believe that in a situation in which very large doses of

steroids have been used, the withdrawal should be rather slow, but not to the extent of reducing the dose by only one milligram per week. If large doses have been used, they can be reduced rather rapidly to 20 or 15 mg. The only untoward feature in these circumstances is a rebound, and generally the rebound will not be too violent as long as the patient is maintained on approximately 20 mg. per day. If withdrawal is sudden, adrenal insufficiency in addition to a rebound will result, which will be too much to handle. The crises that occur with infection and with surgery in these patients are fully as important as those mentioned by Dr. Bayles in patients with rheumatoid arthritis. They should be handled as are diabetics in whom, during infections, more insulin is needed. When on large doses of steroids, such patients require more steroids during the presence of an infection and, in addition, they must be covered through surgery.

Dr. Freyberg will present the last part of this panel and will discuss the various types of steroids. I hope that he will also include a few words about his philosophy on the use of these medications.

DR. RICHARD H. FREYBERG: Since cortisone was inaugurated, continuing efforts have been made by both the clinician and the chemist to eliminate or to lessen the difficulties that arise with the use of the corticosteroids. Those difficulties are usually greater, and more frequently encountered, when the corticosteroids are used over long periods of time, as is required in the treatment of a chronic illness such as rheumatoid arthritis.

Hydrocortisone became the most popular corticosteroid from 1951 through 1955, a period when the chemists were altering the structure of cortisone or of hydrocortisone in different ways, in an endeavor to lessen the undesired effects. The first of the synthetic corticosteroids developed, that had practical advantages, were prednisone and its companion prednisolone.

(Slide) A structural formula will help to orient you regarding some of the changes that were developed in the basic structure of cortisone and of hydrocortisone, which differs from cortisone only in the hydrogen atom added at the C-11 position. Prednisone, with the same basic structure, is different only in that there is desaturation between carbon one and two. Prednisolone is exactly the same as hydrocortisone, except for similar desaturation between C-1 and C-2. These two drugs were used successfully, and they seemed to have greater antirheumatic

effect in doses that were thought to be comparable in other respects. At the same time, there was less sodium retention and resultant edema, fewer complications from hypertension and less loss of potassium from the body. These two drugs became quite popular and largely replaced for oral administration, at least for long-term use, cortisone and the previously popular hydrocortisone. The effect obtained with a milligram of prednisone compared with that obtained with a milligram of hydrocortisone is quite striking. The dosage ratio is about 1 to 4 or 5; that is, one milligram of prednisone will produce antirheumatic effects comparable to four or five milligrams of hydrocortisone, to maintain a plateau of partial suppression of rheumatoid arthritis. If a daily dose of hydrocortisone of 50 to 60 mg. per day was required, only 12 or 15 mg. prednisone is needed. Prednisolone dose requirements and effects were essentially the same as prednisone.

As the use of these drugs increased, the rather higher incidence of peptic ulcer in those patients treated over long periods was recognized. The question arose, and is as yet unanswered, as to whether the incidence was actually increased with the new steroids. The true incidence is very difficult to determine, because patients who had formerly been on hydrocortisone for a few years and then changed to treatment with prednisone or prednisolone for several months, or perhaps even for a year or two, showed some manifestations of ulcer. It was not determined to what degree the hydrocortisone contributed to ulcer formation or to what degree prednisone was implicated. Was there any difference? On the basis of our current knowledge, I don't know how anyone can tell, but it is fairly certain that ulcerogenicity may be involved with the use of prednisone over long periods of time.

There also seemed to be a higher incidence of purpura and ecchymosis in these patients. The incidence is not small, almost 35 to 40 per cent of patients treated for long periods of time. Even with these problems there seemed to be advantages in using prednisone and prednisolone which became more popular than hydrocortisone. There have been continued efforts to improve these preparations. Many attempts were made to add a halogen to the steroid. There was considerable success in increasing certain of the effects, but there also was a great increase in sodium retention. This prevented the halogenated corticosteroid from being a *practical* gain. But when it was discovered that a hydroxyl group could be added to carbon 16 of the hydrocortisone structure,

with fluorine attached to carbon 9, this was overcome. (Slide) This slide shows the formula of 9-alpha-fluoro-16-hydroxy-prednisolone, now called triamcinolone. Over a period of approximately two and a half years, we have had experience with about 200 patients who were given this preparation, and I can say something about its effects.

With regard to dosage, we found that, in a group of patients that had previously received hydrocortisone or prednisone, and then been given triamcinolone, a few required considerably less of the latter drug, many required slightly less, and an occasional patient required slightly more. When averaged out, using triamcinolone di-acetate, 90 per cent of the prednisone dose was required to produce what we consider to be comparable effects. Of triamcinolone alcohol, now commonly used, about 85 per cent of the prednisone dose is required. This alone would account for no practical gain. However, there was another important difference, in that sodium was not retained. Edema did not result, nor was there increased potassium excretion. In patients who could not tolerate previously available corticosteroid because of edema, triamcinolone could be used without resultant edema. Also, there were differences in some of the side effects. Headache occurred more often, sometimes associated with dizziness that was quite troublesome. At times there was dizziness alone.

Many of these patients had anorexia with consequent reduced intake of food. In some patients (but not all), nausea accompanied the anorexia, and these patients developed weight loss and weakness. Among those treated for less than 90 days there were several who lost as much as 7 or 8 per cent of their body weight—weight losses of 10 or 12 pounds. In some patients treated for longer periods, quite significant weight loss occurred. In all patients who are changed from hydrocortisone or prednisone to triamcinolone, there is an initial weight loss because of increased elimination of sodium that has been retained in the body; in most patients a relatively fixed weight is attained after this initial loss. But in some, there is continued weight loss and accompanying weakness, which is quite troublesome. It was necessary to stop the medication in some of these patients.

We now believe that this drug differs from hydrocortisone in at least two respects: one, instead of stimulating the cerebrum, with resultant sense of excitement, there is more often depression; two, it does not stimulate appetite or produce euphoria and a sense of well-

being; instead, in many patients it has just the opposite effect—it causes anorexia. Although this is a detriment in many instances, it may also be used to advantage in certain patients, as will be mentioned later.

Because some of the metabolic differences were considered favorable, we hoped that a decreased incidence of peptic ulcer would result with use of this preparation. Some of our patients who had peptic ulcer, and whose medication was changed to triamcinolone, improved. In some of these the ulcer healed, symptoms subsided and roentgen evidence of the ulcer disappeared, while they were treated with triamcinolone. In those of our patients who had not had ulcer previously, a few developed an ulcer when they were treated with triamcinolone. So, although there *may be* less of a problem with peptic ulcer (and we are not sure that this is a fact), the problem of ulcer still exists, even with the use of triamcinolone.

We also hoped there would be less osteoporosis. Maybe there is, but we do not have good evidence of this yet. More time will be required to find out. Some patients receiving triamcinolone, and no other corticosteroid, have developed severe osteoporosis, and some of these have had compression fractures of vertebral bodies.

Some workers in this field have said that this preparation is of greater benefit in psoriasis than are other steroids. This has not been our experience; but it is possible that this is due to differences in the way this steroid was used.

About the same time that triamcinolone was produced, a methyl group was placed at the carbon-6 position in prednisolone, which resulted in the preparation called methyl prednisolone (Medrol). The effects of methyl prednisolone are about the same as those of triamcinolone, although it has less tendency to produce anorexia and subsequent weight loss; other effects are quite comparable. It is not quite as dependable in preventing sodium retention. The side effects are similar also.

Another preparation available for general use is 9-alpha-fluoro-16-methyl (instead of hydroxyl) prednisone. This preparation is dexamethasone (Decadron) and is much more potent, milligram for milligram, than any previously prepared steroid, and that is about the only difference. Side effects are similar. Some patients become more edematous, develop more fat deposits, and gain more weight with dexamethasone than formerly with other steroids. Also, some of our patients, changed from another corticosteroid to dexamethasone, have done

very poorly on doses much larger than recommended or considered as the average dose of this steroid. This occurred in about 25 per cent of our patients. But there are other patients who do better on dexamethasone than with other corticosteroids. So, we now have six readily available steroids, hydrocortisone, prednisone, prednisolone, triamcinolone, methyl prednisone, and dexamethasone, and we can be selective in the use of these. In a patient with edema we would want to use the steroid least likely to add to the edema—namely, triamcinolone. Or, in treating an obese patient with a ravenous appetite and difficult to reduce in weight, again triamcinolone would be preferred over other steroids. On the other hand, in an undernourished person whose weight should be increased, triamcinolone is not the best choice; it would be hydrocortisone. Hydrocortisone is still an excellent steroid and should not be discarded in favor of other steroids with slightly more milligram per milligram potency. Potency alone is not an advantage, unless the side effects, the effects other than the anti-inflammatory action of the steroid, are less—so that the therapeutic ratio is improved.

The local use of corticosteroids has practical value in some circumstances, particularly in persons who cannot tolerate the drug when given systemically, with resultant difficulty in one or two joints that are particularly troublesome. The medication can be injected directly into these joints. Several corticosteroid preparations are available for such local use. One is hydrocortisone tertiary butyl acetate. This medication has perhaps a somewhat longer effect when injected intra-articularly, but the difference is slight as compared to hydrocortisone acetate. We have found that a dose of approximately 50 mg. is best for large joints such as the knee. Other corticosteroid preparations with a higher potency ratio to cortisone, when given systemically, have proportionally less effect. One cannot give intra-articularly one fourth as much prednisone as hydrocortisone and expect to get a comparable effect. It is necessary to give about the same amount of prednisone derivatives as hydrocortisone, when injected intra-articularly; the same is true with triamcinolone.

Triamcinolone has been further altered by the addition of a side chain combining the oxygens at C-16 and 17; this is the acetonide. This corticosteroid preparation has been found to be somewhat more effective when applied topically to the skin for different forms of dermatitis, and to the eye for certain types of ophthalmitis. Similarly, it

should be better when used intra-articularly. Based upon early studies of potency, it was recommended that only 6 or 8 mg. of this be injected intra-articularly, instead of 50 mg. We tried it. It failed to produce adequate relief in these small doses; we have had to give 30 to 50 mg., and in such doses the results are good, with a more prolonged effect.

It should be pointed out that dexamethasone is dispensed in tablets containing only 0.5 or 0.75 mg., since it is six to eight times as effective as prednisone, and 25 to 30 times as effective as hydrocortisone. The dose requirement is approximately 2 to 4 mg. daily as contrasted with 60 to 80 mg. of hydrocortisone and 12 to 20 mg. of prednisone. One needs to keep these dosage differences clearly in mind.

Other things I could say will very likely be brought out in answers to questions.

MODERATOR RAGAN: We have received a few questions to answer. *Dr. Bayles, do you feel the use of steroids is dangerous in diabetes or in hypertension?*

DR. BAYLES: This has already been commented on. Mild diabetes is aggravated by the use of steroids. Generally speaking, increasing the insulin dose will provide adequate care of the patient. In our experience, moderate dosage of steroids can be given to diabetics with relative safety.

In hypertension it is probably best not to use cortisone or hydrocortisone, but to use a non- or less-sodium retaining drug, such as one of the analogues, and thus circumvent this hypertensive problem. It can also be helped by low sodium intake and other anti-hypertensive measures familiar to most of you.

MODERATOR RAGAN: Dr. Fischel, *what do you suggest as a following therapy when a rebound develops after steroid withdrawal in treatment of rheumatic fever?*

DR. FISCHEL: This depends very much on the nature of the disease prior to the initiation of therapy. With Dr. Frank and Miss Bellows, we have found the rebound to be more severe in recurrent rheumatic fever where there is heart involvement on admission, or where the duration of the disease has been somewhat prolonged—more than two weeks, for example—before this type of therapy was started. With evidence of rebound, we would reinstitute salicylate therapy. It is certainly not effective in all cases, but it may minimize the severity of the rebound. If carditis is present I would reinstitute cortisone in rather high dosage

to effect suppression as quickly as possible. Unfortunately, once the rebound starts, it seems to have a certain momentum of its own, and it is hard to arrest a flare-up of inflammatory reaction. In the Cooperative Study, one patient who had not previously had heart failure, had a rebound which snowballed. Very severe congestive failure developed, although large doses of cortisone were reinstituted, and the patient died. This is a very sobering aspect of the flare-up of rheumatic inflammation following cessation of therapy. We prefer to avoid it if we possibly can. In that situation, continued suppressive medication with salicylate might have minimized the severity of the rebound, although this cannot be proved.

MODERATOR RAGAN: Dr. Freyberg, this is really two questions: *Can steroids be helpful in osteoarthritis, and when should joints be injected?*

DR. FREYBERG: If it is recognized that the nature of osteoarthritis is primarily that of a degenerative joint disease, and that there is little or no inflammation, and if one realizes that corticosteroids are of benefit to patients with arthritis, chiefly, if not only, because of the anti-inflammatory effects that they produce, the answer to this question is obvious. One would not expect to observe any benefit if one gave corticosteroids in a condition that was not inflammatory in nature. There are occasional exceptions, but they are rare, in my experience. I would find no fault with the administration of a small amount of steroid, less than "aspirinoid" as defined by Dr. Bayles, in a patient with osteo-arthritis, for the stimulating or euphoria-producing effect it has, but not for a substantial anti-rheumatic effect in this non-inflammatory joint disease.

There is just as much difficulty in determining when a joint should be injected as there is in deciding when a patient with rheumatoid arthritis should receive corticosteroid systemically; but there are many instances in which there are clear-cut advantages in the intra-articular use of steroid. In answer to the question asked about a diabetic: if you do not wish to, or cannot manage the diabetes when corticosteroid is given systemically, and if there is much disability from inflammation in one or two of the larger joints, that patient can be helped a lot by giving corticosteroid intra-articularly as needed. There are other situations where there are contraindications, or relative contraindications, for systemic use of steroids, where local use may be helpful. It should be emphasized that one cannot predict how much or how prolonged

the benefit from intra-articular corticosteroid will be in any individual. This can be determined only by trial; if pain is relieved and increased function results, the patient will come back and say, "I want some more intra-articular corticosteroid." An intelligent patient can be relied upon to judge the practical benefit obtained with injection of intra-articular corticosteroid.

MODERATOR RAGAN: Dr. Bayles, two persons in the audience know about *the effect of chloroquine on the potentiating effect of steroids, and the effect of chloroquine or Plaquenil. Have you had any experience with these?*

DR. BAYLES: I believe the only controlled experiments that may have any significance are those of Drs. Calkins and Cohen and a small group of patients used by Dr. Bagnall as a control. As yet, I do not even know my own conclusions about these drugs. Chloroquines, and I prefer hydroxy-chloroquine or Plaquenil because it is less toxic, causing less dizziness, nausea and other side effects, do have an anti-inflammatory effect in rheumatoid arthritis. Since, as I pointed out earlier, we use practically no steroids, I have had no experience with this. In a few patients with non-renal disseminated lupus that I followed, it seemed to me that Plaquenil was effective in controlling symptoms. I don't think the disease was cured in any sense, but there were suppressive effects. Nor do I think the answer is at hand. In the long-term use of these drugs, we have seen leukopenia, skin rashes, and other disturbing things following the use of antimalarials.

MODERATOR RAGAN: The most disturbing thing we have seen with the use of chloroquine has been the appearance of corneal opacities, as reported in the *J.A.M.A.* Apparently, the drug is deposited in the cornea. At least it fluoresces under a slit lamp. It disappears when the chloroquine is discontinued, but it is quite disturbing. *Have you any comments about the antimalarials, Dr. Freyberg?*

DR. FREYBERG: Any comments which I could make now are not based upon a careful statistical analysis now in progress. I have been disappointed in how seldom chloroquine or hydroxy-chloroquine appears to benefit patients with rheumatoid arthritis when used alone, or to be instrumental in lowering the amount of corticosteroid required when it is used. But, on the other hand, I have been favorably impressed by its benefit to patients with the syndrome called systemic lupus erythematosus.

MODERATOR RAGAN: We don't think it does much in systemic lupus erythematosus. *How about steroids and gold, Dr. Freyberg? Do you think they fit together? Can they be used together?*

DR. FREYBERG: They can be used together. There is some confusion. Dr. Traeger, one of those who helped to study cortisone derivatives after they became available, is here with us tonight. He and his group first believed that there might be an interfering effect of one of these preparations, one with the other.

When gold therapy was used, the benefits did not occur often and were not observed to as great a degree as when we used steroids. However, I think that there is greatly limited practical advantage in using corticosteroids and gold. If corticosteroids are to be used, the problems that arise from their use must be faced. Similarly, gold therapy presents its own set of problems. Some of these might be masked by the counteracting effect of corticosteroid and may later produce complications. For these reasons I don't like to use them together.

I regard gold as a good drug, and for many patients it is quite adequate and satisfactory as a suppressive agent. I believe corticosteroids are not necessary in such cases. If gold fails, then, after considering the benefits to be had against the potential difficulties that may arise, and after deciding that the risks are outweighed by the advantages to be expected, I use the corticosteroids and use them alone. A number of patients, when given a corticosteroid, have done poorly on it, and there is always the problem of withdrawal. In this situation I often time the giving of the gold therapy to overlap the withdrawal of the corticosteroid.

MODERATOR RAGAN: Here is an iconoclastic question: *Do steroids do any good in rheumatic carditis?*

DR. FISCHEL: I think they do. Many procedures do, but, as with all biological phenomena, they are not 100 per cent effective. Everyone has some failures with them. When we recognize that some failures will occur with a disease as variable as the rheumatic diseases, we shall have a little more consideration for what drugs can do and cannot do, which is a healthier attitude than unbridled enthusiasm or uncritical pessimism.

MODERATOR RAGAN: I shall answer this question. "*Gout and rheumatoid arthritis do not co-exist, as stated by Dr. Bauer. Is there any recent evidence?*" I think they do co-exist.

DR. FREYBERG: I agree, they may.

MODERATOR RAGAN: *Can steroids be used in a patient who has a peptic ulcer before treatment, if the indications are overwhelming?* I should go ahead and use it and try to control the peptic ulcer to the best of my ability. Such indications have to be pretty overwhelming. Would you agree with that?

DR. FREYBERG: Don't you think all contraindications ought to be considered relative, not absolute contraindications? The only absolute contraindication is existence of hypercortico-adrenalism.

MODERATOR RAGAN: *Is* ACTH *as effective as cortisone in rheumatoid arthritis?* I believe everybody but Dr. West in Sheffield, England, thinks they are about equal. He thinks ACTH somewhat more effective, but it is a nuisance to continue the patient on ACTH indefinitely. The chances of causing a buttock abscess are about 100 per cent.

DR. FREYBERG: It should also be pointed out that many physicians believe they should use ACTH, to prevent cortical adrenal atrophy and hypofunction. If this is done, one is just substituting hypopituitarism for the hypofunctioning adrenal, and in the end one has similar if not the same problems.

MODERATOR RAGAN: I think it is fair to say that a reasonable number of patients who have been given ACTH weekly or three days in every month, will develop sensitiveness to either hog or bovine ACTH and then one is in trouble. So, by and large, we don't use it.

DR. FREYBERG: I think another word is appropriate. The patient with rheumatoid arthritis, who greatly needs an anti-inflammatory effect, is not benefited much by a once-weekly injection of corticotropin-zinc. It needs to be given once or twice a day, and how often is the patient with such chronic illness willing to be injected?

MODERATOR RAGAN: Dr. Bayles, *you sometimes use "aspirinoid" dose type of therapy with steroids. Have you seen osteoporosis develop when this procedure is followed in small maintenance doses?*

DR. BAYLES: My answer would be that we don't use steroids at all, except in the few areas that I mentioned and, when indicated, I would use it in this type of dosage. We have certainly seen vertebral collapse and osteoporosis develop on 20 mg. of prednisone a day, which is a pretty heavy dose in my opinion. Therefore, I think that over a long period of time small amounts could produce osteoporosis.

MODERATOR RAGAN: Do you agree with that, Dr. Freyberg?

DR. FREYBERG: Corticosteroids are among the many factors that will

contribute to osteoporosis. They are very potent additional factors and sometimes are "the straw that breaks the camel's back",—more correctly, the human's back. One of the most feared ill effects is that the patient will acquire a compression fracture of a vertebra as a result of continued use of corticosteroid. I am not sure that we can prevent this. Good prophylaxis is the important consideration.

MODERATOR RAGAN: I, too, am not sure we can prevent this complication by good prophylaxis. The problem we face is that, if the steroids are withdrawn because an osteoporotic vertebra becomes compressed, the patient may end up bedridden and will become more osteoporotic. In our experience, we have become greatly concerned about this and employ a variety of manoeuvers to brace the patient's back and we have been gratified that, in almost every instance, pain has subsided in about two to three weeks. So far, nobody has transsected the cord. It is a harrowing sight to see a patient with three, four or five compressed vertebrae. As Dr. Bayles said, we have a big bear by the tail. From our experience, I am fairly convinced that the use of androgens, even Nilevar, has not modified this picture. How much of this is due to the fact that one is giving steroid to an osteoporotic individual who is not walking, I am not prepared to say. In the experimental animal, the rat for example, it is very difficult to achieve doses of steroid which will produce decalcification, but there is no question that one of the common complications of Cushing's syndrome is a compressed vertebra.

DR. FREYBERG: Could I interrupt to ask a question which seems important to me? I would like to ask each member of our panel how he feels concerning the ulcerogenic process of corticosteroids. Recently, a very distinguished physician gave a report in which he concluded that there is "no evidence" that corticosteroids cause, or contribute to, the formation of peptic ulcer. Based on the results of our studies, I vehemently disagree with this opinion. When we were searching for them we found x-ray evidence indicating that about 30 per cent of patients with a prolonged corticosteroid therapy had peptic ulcer—not all of these were symptomatic. I wish to hear what each panel-member thinks.

DR. BAYLES: I have no statistical answer, Dr. Freyberg, but I am old enough to remember the pre-ACTH-cortisone days when peptic ulcer was certainly not the problem in rheumatoid arthritis that it is now, with hemorrhage, perforation and so forth.

MODERATOR RAGAN: Dr. Fischel.

DR. FISCHEL: I would have to agree. In my own limited experience it seems to have been a common occurrence, and certainly, while ulcer probably exists more commonly among children than is generally recognized, it has become more manifest under steroid therapy. But there, of course, steroids are not used for as long a period of time.

MODERATOR RAGAN: I think it is fairly self-evident that we are seeing more peptic ulcer in patients treated with steroids, but I would like to know how many of these steroid-treated patients never had salicylates. In England they are now disturbed because they have been able to show that melena develops with the administration of plain aspirin. They have done this by a very elegant technique using chromium-tagged red cells and then counting the stool. Approximately 10 cc. of blood may be excreted in the stool per day by a person taking aspirin. There is no blood in the stool when coated aspirin is taken. We have no data on the incidence of peptic ulcer in the pre-steroid era. Nobody was interested in them. I would seriously question Dr. Bauer's data of 8 per cent. This was during the period when the patient was asked if he ever had had an ulcer. We know we have to pick up the ulcer when complaints are present, and we see such cases much more frequently than we used to see in our patients with rheumatoid arthritis. When studying this as a group of patients on steroids, our data agree exactly with Dr. Freyberg that 35 per cent of our patients on steroids since 1949 have had a peptic ulcer. We know that in the post-mortem studies, pre-steroid, peptic ulcer was not seen very commonly. Certainly it is now seen much more commonly. The whole situation is muddy. We cannot give accurate data, but we can say that it is a clinical impression that a peptic ulcer is seen more frequently in rheumatoid arthritis since the use of steroids.

We have one more question before our time is up, concerning the influence of steroids on the function of the thyroid and the gonads. In the dosage in which steroids are usually given for the management of long-continued control of rheumatoid arthritis, I believe they have no effect.

DR. FREYBERG: I agree.

MODERATOR RAGAN: That is the end of our program, and I thank you all very much.

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Monday **CLINICAL ASPECTS OF GENETICS**

October 23 *Moderators:* MELVIN M. GRUMBACH, ALEXANDER G. BEARN

Speakers: ALEXANDER G. BEARN, MELVIN M. GRUMBACH, PARK S. GERALD, ORLANDO J. MILLER, HELEN M. RANNEY, THEODOSIUS DOBZHANSKY, Ph.D.

Tuesday **RHEUMATOID ARTHRITIS**

October 24 *Speakers:* RICHARD H. FREYBERG, CHARLES L. CHRISTIAN, ROBERT C. MELLORS

SYSTEMIC LUPUS ERYTHEMATOSUS

Speakers: STANLEY L. LEE, DANIEL L. LARSON, JANE H. MORSE

Wednesday **CARCINOMA OF THE CERVIX UTERI**

October 25 *Moderator:* MICHAEL J. JORDAN

Speakers: EMERSON DAY, MYRON R. MELAMID, RUTH J. GUTTMAN, GRAY H. TWOMBLY

TREATMENT OF CANCER OF THE BREAST

Moderator: DAVID B. HABIF

Speakers: CUSHMAN D. HAAGENSEN, JOSEPH H. FARROW, ANTHONY R. CURRERI

Thursday **EDEMA FORMATION AND MOBILIZATION**

October 26 *Moderator:* ALFRED P. FISHMAN

Speakers: GEORGE E. PALADE, FRANCIS P. CHINARD, ROBERT F. PITTS, WILBUR H. SAWYER, WALLACE W. McCRORY, JAMES O. DAVIS, JOHN H. LARAGH, MARVIN F. LEVITT

Friday **CONFERENCE ON LIVER DISEASE**

October 27 *Moderator:* HANS POPPER

Speakers: FENTON SCHAFFNER, OSCAR BODANSKY, FRANCIS F. RUZICKA, SAUL KRUGMAN, THOMAS C. CHALMERS, JR., SYDNEY S. GELLIS

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CARDIOVASCULAR SYSTEM

September 12

THE MECHANISM AND RECOGNITION OF HEART MURMURS

J. SCOTT BUTTERWORTH
Associate Professor of Medicine
New York University Post-Graduate Medical School

ANATOMIC AND HEMODYNAMIC INTERRELATIONSHIP IN HEART MURMURS

BERTHA RADER
Assistant Professor of Medicine, New York University School of Medicine

September 18 **(Monday)**

NEWER PHYSIOLOGICAL METHODS IN DIAGNOSIS OF HEART DISEASE

EUGENE BRAUNWALD
National Heart Institute, Bethesda, Maryland

NEWER RADIOLOGICAL METHODS IN DIAGNOSIS OF HEART DISEASE

RICHARD S. ROSS
Associate Professor of Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

September 26

ANATOMICAL AND PHYSIOLOGICAL FACTORS IN CONGENITAL HEART DISEASE

MARY A. ENGLE
Assoc. Professor of Pediatrics, Cornell University Medical College

CARDIAC SURGERY IN CONGENITAL HEART DISEASE

ELLIOTT S. HURWITT
Clinical Professor of Surgery
College of Physicians and Surgeons, Columbia University

October 3

MEDICAL HYPOTENSION AND SHOCK

DICKINSON W. RICHARDS
Samuel W. Lambert Professor of Medicine
College of Physicians and Surgeons, Columbia University

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Lanesta Gel has complete esthetic acceptance and is well tolerated.

*Gamble, C. J.: Am. Pract. & Digest Treat. *11*:852 (Oct.) 1960. See also Berberian, D. A., and Slighter, R. G.: J.A.M.A. *168*:2257 (Dec. 27) 1958; Olson, H. J.; Wolf, L.; Behne, D.; Ungerleider, J., and Tyler, E. T.: California Med. *94*:292 (May) 1961; Kaufman, S.A.: Obst. & Gynec. *15*:401 (Mar.) 1960; Warner, M.P.: J.Am. M. Women's A. *14*:412 (May) 1959.

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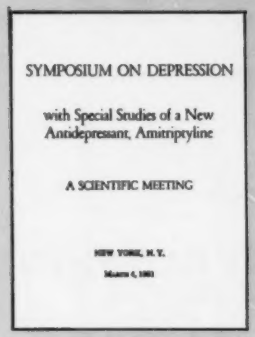


EXCERPTS FROM A SYMPOSIUM ON DEPRESSION

ELAVIL®

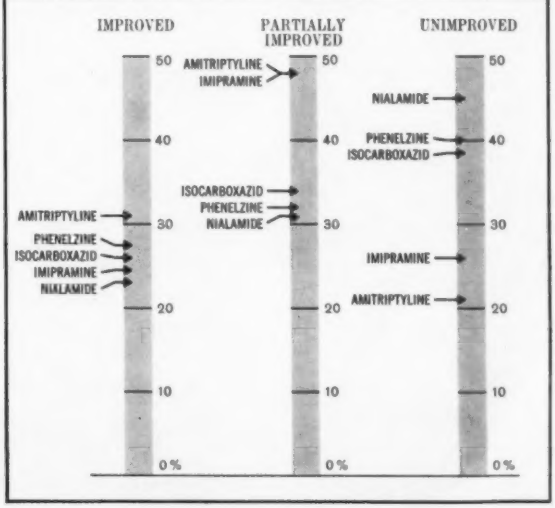
AMITRIPTYLINE HYDROCHLORIDE

INVESTIGATOR	FINDINGS
DUNLOP, EDWIN: The treatment of depression in private practice.	"Amitriptyline [ELAVIL] has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears . . . to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes. ". . . Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders."
BENNETT, DOUGLAS: Treatment of depressive states with amitriptyline.	"In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation. The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression."
SAUNDERS, JOHN C.: Antidepressives: the pith of affective therapy.	"Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuropsychiatric diseases. . . . Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75)."
OSTFELD, ADRIAN M.: Effects of an antidepressant drug on tests of mood and perception.	"Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population."

(This symposium was published in Diseases of the Nervous System, Volume 22, Section Two—Supplement, May 1961)

INVESTIGATOR	FINDINGS
AYD, FRANK J., JR.: A critique of antidepressants.	"Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine. "... Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments."

COMPARISON OF THERAPEUTIC RESULTS WITH VARIOUS ANTIDEPRESSANTS



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EXCERPTS FROM A SYMPOSIUM ON DEPRESSION (continued)

ELAVIL®

AMITRIPTYLINE HYDROCHLORIDE

INVESTIGATOR	FINDINGS
DORFMAN, WILFRED: Masked depression.	"In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%)."
FELDMAN, PAUL E.: Psychotherapy and chemotherapy (amitriptyline) of anergic states.	"Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings."

INDICATIONS: manic-depressive reaction—depressed phase; involutional melancholia; reactive depression; schizoaffective depression; neurotic-depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whether the emotional difficulty is a manifestation of neurosis or psychosis,[1] and in ambulatory or hospitalized patients.[1,2,3]

USUAL ADULT DOSAGE: Tablets — initial dosage 25 to 50 mg. three times a day, depending on body weight, severity, and clinical disturbances. Dosage may be adjusted up or down depending upon the response of the patient. Some patients improve rapidly, although many depressed patients require four to six weeks of therapy before obtaining antidepressant response. For the ambulatory patient the dosage range for Tablets ELAVIL is 40 to 150 mg. daily. In the hospitalized patient, a daily dosage up to 300 mg. may be required. Injection ELAVIL may be given IM to rapidly calm depressed patients with symptoms of anxiety and tension while instituting therapy of the underlying depression. Initial therapy is 2 to 3 cc. (20 to 30 mg.) IM, q.i.d.

The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. It does, however, augment or may even potentiate the action of MAO inhibitors. Thus, in patients who have been receiving MAO inhibitors, ELAVIL should be instituted cautiously after the effects of the MAO inhibitors have been dissipated. No evidence of drug-induced jaundice, agranulocytosis, or extrapyramidal symptoms has been noted. Side effects with ELAVIL are seldom a problem and are not serious. They are dosage-related and have been readily reversible. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma, prostatic hypertrophy and urinary retention.

SUPPLY: Tablets, 10 mg. and 25 mg., in bottles of 100 and 1000. **Injection** (intramuscular), in 10-cc. vials, each cc. containing 10 mg. amitriptyline hydrochloride, 44 mg. dextrose, 1.5 mg. methylparaben, 0.2 mg. propylparaben, and water for injection q.s.

REFERENCES: 1. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 2. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 3. Barsa, J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

Before prescribing or administering ELAVIL, the physician should consult the detailed information on use accompanying the package or available on request.

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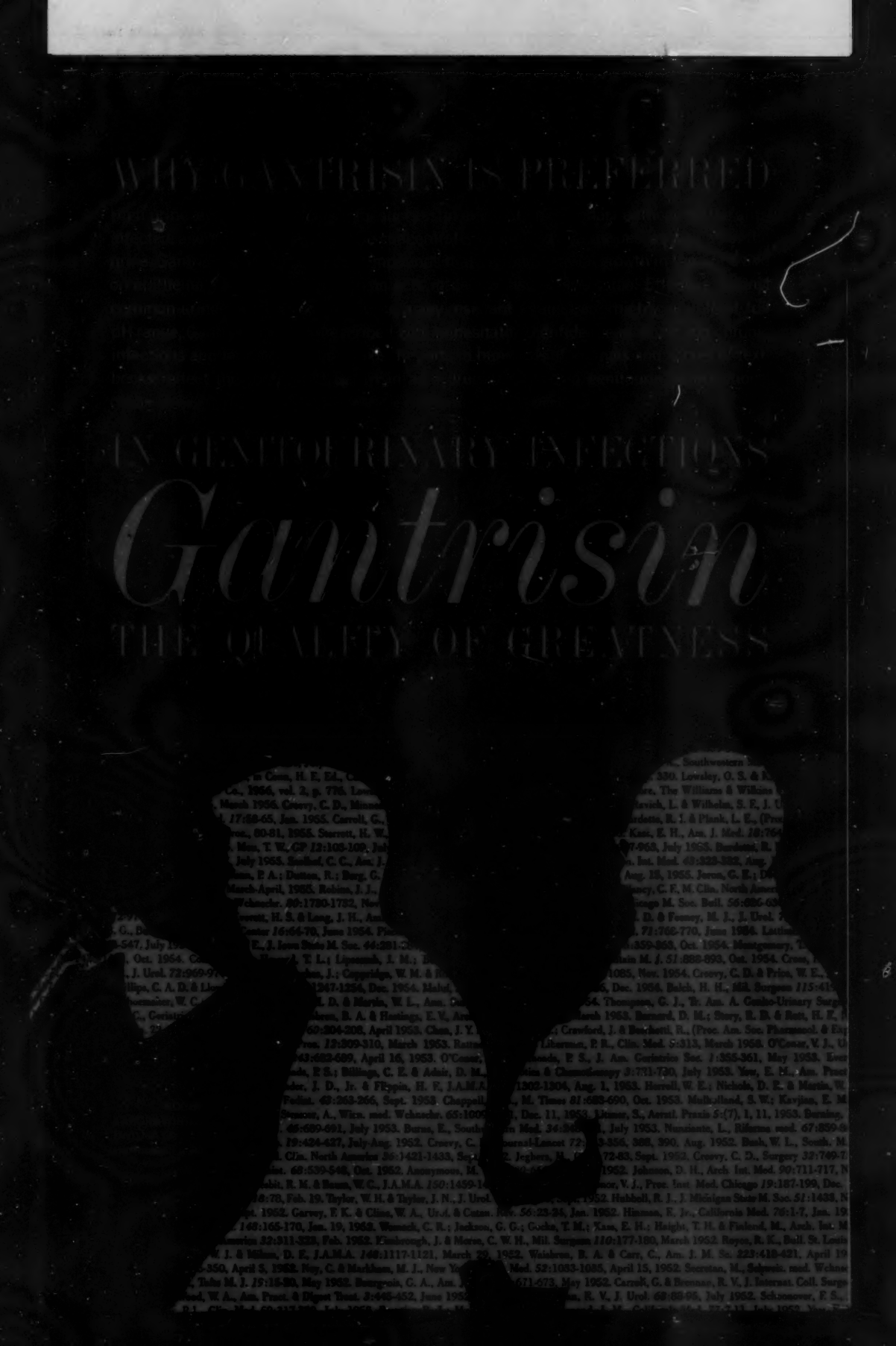
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